exposure to the substance. The profiles include references to scientific literature used to support the listings. The substances listed in the RoC do not include all human carcinogens. The RoC lists only those nominated agents, substances, mixtures, or exposure circumstances for which relevant data exist and have been reviewed and found to meet the listing criteria defined above. As additional substances are nominated, they will be considered and reviewed for possible listing in future editions of the RoC.

Other Information Provided in the *Twelfth Report on Carcinogens*

Following the Substance Profiles, additional information is provided about terms that are used frequently in the profiles, including a Glossary, a list of Acronyms and Abbreviations, and Units of Measurement. In addition, the following appendices are provided:

- Appendix A provides a list of manufacturing processes, occupations, and exposure circumstances classified by IARC as carcinogenic to humans.
- Appendix B lists the agents, substances, mixtures, or exposure circumstances that have been delisted from the RoC.
- Appendix C lists the agents, substances, mixtures, or exposure circumstances that have been reviewed but not recommended for listing in the RoC.
- Appendix D identifies participants who collaborated in preparation of the *Twelfth Report on Carcinogens.*
- Appendix E is a table of chemicals that have been nominated to the NTP for toxicological or carcinogenicity testing since 2004.
- Appendix F is a cross-referenced list of substances and their common synonyms or abbreviations.
- Appendix G lists, by Chemical Abstract Service (CAS) Registry number, all of the chemicals included in the RoC for which CAS Registry numbers were identified.

The *Twelfth Report on Carcinogens* was prepared following procedures that maximized the quality, objectivity, utility, and integrity of the information contained in the report. Although not anticipated, factual errors or omissions in this report may be identified after its distribution. If this should happen, these errors or omissions will be addressed by the NTP. Where appropriate, corrections will initially be posted on the NTP RoC Center Web site at http://ntp.niehs.nih.gov/go/roc and then made in the next edition of the RoC. For more information on the published *Twelfth Report on Carcinogens*, including how to request a printed or electronic copy or to access it on the Internet, visit the NTP RoC Center Web site at the link provided above or contact Dr. Ruth Lunn, Director, Report on Carcinogens Center, National Toxicology Program, MD K2-14, P.O. Box 12233, Research Triangle Park, NC 27709; telephone (919) 316-4637; fax (919) 541-0144; e-mail lunn@niehs.nih.gov.

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Web Sites

American Conference of Governmental Industrial Hygienists (ACGIH)
http://www.acgih.org/home.htm

Code of Federal Regulations (CFR), U.S. Government Printing Office
http://www.gpoaccess.gov/cfr/index.html

Consumer Product Safety Commission (CPSC)
http://www.cpsc.gov

Department of Transportation (DOT)
http://www.dot.gov

Environmental Protection Agency (EPA)
http://www.epa.gov
Integrated Risk Information System: http://cfpub.epa.gov/ncea/iris/index.cfm

Food and Drug Administration (FDA)
http://www.fda.gov
Center for Food Safety & Applied Nutrition: http://www.cfsan.fda.gov

International Agency for Research on Cancer (IARC).
http://www.iarc.fr
Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans
http://monographs.iarc.fr/index.php

National Institute for Occupational Safety and Health (NIOSH)
http://www.cdc.gov/niosh
Pocket Guide to Chemical Hazards: http://www.cdc.gov/niosh/npg
NIOSH Safety and Health Topic – Cancer: http://www.cdc.gov/niosh/topics/cancer
NIOSH Carcinogen List: http://www.cdc.gov/niosh/topics/cancer/npotocca.html

National Toxicology Program (NTP)
http://ntp.niehs.nih.gov
Report on Carcinogens: http://ntp.niehs.nih.gov/go/roc

Occupational Safety and Health Administration (OSHA)
http://www.osha.gov

NTP Report on Carcinogens Review Process

The Report on Carcinogens (RoC) is a Congressionally mandated document that identifies and discusses agents, substances, mixtures, or exposure circumstances (collectively referred to as "substances") that may pose a hazard to human health by virtue of their carcinogenicity. Substances are listed in the report as either *known* or *reasonably anticipated to be human carcinogens*. The National Toxicology Program (NTP) prepares the RoC on behalf of the Secretary of Health and Human Services (HHS). The RoC review process is described below and consists of four major parts: (1) nominations and selection of candidate substances, (2) scientific review of candidate substances, (3) peer review of draft substance profiles, and (4) preparation of the RoC and transmittal to Congress and the public. A schematic of the RoC review process is provided at the end of this section.

Nominations and Selection of Candidate Substances

The NTP invites nominations for consideration for listing in the RoC from anyone in the public and private sectors. Nominations may seek to list a new substance in the RoC, reclassify the listing status for a substance already listed, or remove a substance already listed. Nominations should be submitted to the NTP[1] at http://ntp.niehs.nih.gov select "Provide Input to NTP." Nominations must contain a rationale or reason for the review and, if possible, appropriate background information and relevant data (e.g., journal articles, NTP Technical Reports, International Agency for Research on Cancer Monographs, exposure surveys, and release inventories) to support the rationale.

The NTP initially evaluates each nomination to determine whether the scientific information available for a nomination justifies its formal review and consideration. Those nominations proposed for review proceed as discussed below. The reason for not going forward with review of a new nomination would be the lack of sufficient information[2] for applying the listing criteria[3] (see Introduction). The reason for not proceeding with a nomination to reclassify or remove a current listing would be the absence of significant new scientific information published since the original listing. Those nominations not selected for review are returned to the original nominator who is invited to resubmit the nomination with additional information such as new data, exposure information, etc. that justifies a formal review. The NTP may defer or terminate the review of a proposed nomination at any time if relevant information becomes available that warrants the NTP's reconsideration of the substance's review. In such cases, the nominator, the NTP Board of Scientific Counselors (BSC),[4] the NTP Executive Committee,[5] and the public would be notified of this action.

The NTP announces nominations proposed for review and solicits its public comments through announcements in the *Federal Register* and NTP publications. These announcements ask for relevant information concerning carcinogenicity of the substance as well as data on current production and information on exposure and patterns of use. Comments received in response to the public announcements are used to (1) refine the list of nominated substances to identify the candidate substances that will proceed through the full review process and (2) identify scientific issues that should be addressed in the preparation and/or review of the draft background document for an individual candidate substance. In addition, the NTP invites the public to nominate scientists to serve on an expert panel[6] for each specific candidate substance. An expert panel will be convened to provide peer review of the draft background document, make a recommendation for the candidate substance's listing status in the RoC, and provide the scientific justification for that recommendation.

Scientific Review of Candidate Substances

The scientific review of a candidate substance consists of three major steps: (1) preparation of the draft background document, (2) review by an expert panel at a public meeting, and (3) internal review by two independent federal committees.

Draft Background Documents

The NTP prepares a draft background document for each candidate substance under consideration. The background documents may be prepared with the assistance of a consultant(s) with expertise and/or knowledge relevant to the specific candidate substance. Background documents are prepared following the general format presented below. Background documents do not contain any opinion regarding the listing status for the candidate substance. Data used to prepare Sections 3 through 5 must come from publicly available, peer-reviewed sources.

1. Introduction

This section describes the properties (e.g., chemical, physical or biological) of the candidate substance and states the scientific rationale for review. For chemicals, it contains the following sections (1) chemical identification, including synonyms, trade names, CAS Registry numbers, molecular formula, and molecular structure, (2) physical-chemical properties, and (3) identification of structural analogues or metabolites. For other types of agents (e.g., biological, exposure circumstances, or physical), it provides appropriate information to define the candidate substance.

2. Human Exposure

This section provides a summary of relevant data documenting both present and past exposures. It typically provides information on use, production, environmental occurrence, and exposure (including release and fate in air, water, soil, and food), exposure to the general population (e.g., occurrence in consumer products or medical devices), occupational exposure, biological indices of exposure, and regulations and guidelines to limit exposure.

3. Human Cancer Studies

This section summarizes traditional cancer epidemiology studies (mainly case-control and cohort studies, but may also include descriptive studies and case reports). Data from clinical studies may also be included.

[1]National Toxicology Program, Report on Carcinogens Center, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709.

[2]Lack of sufficient information means that adequate studies (such as animal, human, or mechanistic), which are critical for evaluation of the carcinogenicity of the nomination, are not currently available in the peer-reviewed literature.

[3]The criteria for listing a substance in the RoC are available at http://ntp.niehs.nih.gov see "Report on Carcinogens."

[4]The BSC is a federally chartered advisory committee whose members are appointed by the Secretary, HHS. The BSC provides advice to the NTP Director on matters relating to scientific program content and evaluates the scientific merit of the NTP's intramural and collaborative programs.

[5]The NTP Executive Committee is composed of the heads (or their designees) of federal research and regulatory agencies and provides advice to the NTP on policy issues.

[6]An expert panel is an *ad hoc* group of scientists with relevant expertise and knowledge selected by the NTP from the public and private sectors. Nominations to serve on specific expert panels are solicited from federal and nonfederal sources. The final selections for membership are based upon providing a balanced and unbiased group of highly qualified individuals and are made in accordance with the Federal Advisory Committee Act and HHS implementing regulations.

4. Studies in Experimental Animals

This section summarizes experimental animal studies of potential carcinogenesis including long term bioassays, subchronic studies, initiation and promotion studies, and studies of known metabolites.

5. Other Relevant Data

This section discusses the available, relevant mechanistic and other scientific information that would be needed to understand the toxicity and potential carcinogenicity of the candidate substance and that would be useful for evaluating the carcinogenic potential of the substance in people. For a specific substance, it may include information on (1) absorption, distribution, excretion and metabolism, (2) genetic damage and related effects, (3) mechanistic studies and considerations, (4) toxicity, and (5) the carcinogenicity and mutagenicity of structural analogues.

When the initial draft is completed, the NTP posts the draft background document on the RoC Web site. Availability of the draft background document is announced on the NTP listserv and in other NTP publications. Draft background documents are also available on compact disks or in hardcopy upon request (see Contact Information, below).

Expert Panel Meeting

The NTP convenes an expert panel for each candidate substance. The NTP publishes a *Federal Register* notice at least 60 days prior to the expert panel meeting announcing the meeting and availability of the draft background document. The public is invited to attend this meeting and provide oral and/or written comments on the draft background document. The public may also provide opinion on the listing status for the candidate substance. All comments received within this time period become part of the public record that will be reviewed by the expert panel and are posted on the RoC Web site. The expert panel is first charged to peer review the background document. Once the peer review is complete, the NTP asks the expert panel (1) to apply the RoC listing criteria to the relevant scientific evidence and make a recommendation regarding the listing status for the candidate substance and (2) to provide the scientific justification for that recommendation. The expert panel will also submit a report that contains (1) its peer review comments on the draft background document and (2) its recommendation for listing in the RoC and the scientific justification for that recommendation. The NTP will post the expert panel's report on the RoC Web site and publish a *Federal Register* notice inviting comment on the expert panel's recommendation for listing status and the scientific justification for that recommendation. The NTP will also prepare a response to the expert panel's peer review comments on the draft background document that will be made available to the public on the RoC Web site upon release of the RoC.

Following the expert panel meeting, NTP staff reviews and considers the expert panel's peer review comments and any public comments as it finalizes the background document on the candidate substance. The final version of the background document is then posted on the RoC Web site. Availability of the final background document and the expert panel report is announced through the NTP listserv.

Internal Reviews by the Government

Following the expert panel meeting, the NTP goes through a number of reviews that are internal to the government to develop an initial listing status for each candidate substance to the RoC. The internal review process is closed to the public and consists of separate meetings of two groups: (1) an interagency scientific review group (ISRG) and (2) the NIEHS/NTP scientific review group (NSRG). Both groups are provided with all relevant information (including the background document, the expert panel report, and any public comments received to date) on the candidate substances and asked to apply the listing criteria to this information and make a recommendation on the listing status of the candidate substance.

Peer Review of Draft Substance Profiles

Taking into consideration the listing recommendations of the expert panel, the NSRG, and the ISRG, and the public comments, the NTP prepares a draft substance profile[1] with a listing recommendation for each candidate substance. Once the draft substance profile is developed, the NTP convenes a meeting of the BSC to peer review the draft substance profiles for candidate substances to the RoC. The NTP publishes a *Federal Register* notice at least 60 days prior to the BSC meeting announcing the meeting and the availability of the draft substance profiles. The public is invited to attend this meeting and provide oral and/or written comments on the draft substance profiles. All comments received within this time period become part of the public record for review by the BSC and posted on the RoC Web site. The NTP makes available to the BSC all relevant information. The BSC is charged to determine whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated and supports the NTP's policy decision regarding its listing in the RoC. The BSC is not asked to review the NTP's decision regarding listing status. The BSC prepares and submits a peer review report to the NTP that describes the nature and scope of its findings and conclusions concerning the NTP's draft substance profiles.

Preparation of Draft RoC and Transmittal

The NTP responds to the peer review report and drafts the next edition of the RoC. The draft RoC is submitted to the NTP Director for review. The Director distributes the draft RoC to the NTP Executive Committee for consultation, review, and comment. Following approval of the draft RoC by the Director, a final draft of the RoC is prepared and submitted to the Secretary, HHS for review and approval. Upon approval of the RoC, the Secretary transmits it to the U.S. Congress, and the report is published and disseminated to the public. The NTP publishes a notice in the *Federal Register* and NTP publications that announces availability of the report and identifies the listing outcome for each candidate substance that underwent formal review for the RoC. At this time, the NTP posts the BSC's peer review report, the NTP's response to that report, and the NTP's response to the expert panel peer review comments on the draft background documents on the RoC Web site. In addition, for the *Twelfth Report on Carcinogens,* the NTP will prepare a response to public comments received on candidate substances since issuance of the expert panel report[2] and will post the response on the RoC Web site.

The NTP makes the latest edition of the RoC available electronically on the NTP RoC Web site (http://ntp.niehs.nih.gov and select "Report on Carcinogens"), on compact disk, and in printed form. For information on how to request a printed or electronic copy, contact Dr. Ruth M. Lunn.

[1]The RoC contains substance profiles for each candidate substance. Full substance profiles are developed for substances *known* or *reasonably anticipated to be human carcinogens* and contain the listing status, summarize the scientific information that supports the recommendation, and provide information on use, exposure and production. Limited substance profiles are developed for candidate substances not listed in or delisted from the RoC, which vary in content on a case-by-case basis.

[2]The NTP's preparation of a response to public comments will be done on a trial basis for the *Twelfth Report on Carcinogens.* The NTP will assess the merit of responding to public comments following completion of the *Twelfth Report on Carcinogens* and determine whether any change is needed in the review process with regard to this practice.

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NTP Listserv

The NTP listserv is an e-mail distribution list used to disseminate information on NTP activities. To subscribe, visit http://ntp.niehs.nih.gov and select "Contact Us."

Report on Carcinogens

Substances Listed in the Twelfth Report on Carcinogens

Listing Status

Substance Profiles

Glossary

Acronyms and Abbreviations

Units of Measurement

Substances Listed in the Twelfth Report on Carcinogens

Bold entries indicate new or changed listings in the Twelfth Report on Carcinogens.

Known To Be Human Carcinogens

Reasonably Anticipated To Be Human Carcinogens

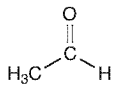
Acetaldehyde

CAS No. 75-07-0

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as ethanal



Carcinogenicity

Acetaldehyde is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to acetaldehyde by inhalation caused tumors in two rodent species and at two different tissue sites. In rats of both sexes, it caused cancer of the nasal mucosa (squamous-cell carcinoma and adenocarcinoma), and in hamsters of both sexes, it caused cancer of the larynx (carcinoma) (IARC 1985, 1987). Inhalation of acetaldehyde also promoted the induction of respiratory-tract tumors by intratracheal instillation of the known carcinogen benzo[*a*]pyrene in hamsters of both sexes.

Since acetaldehyde was listed in the *Sixth Annual Report on Carcinogens,* an additional study in rats has been identified. Administration of acetaldehyde in drinking water increased the incidences of hemolymphoreticular cancer (leukemia and lymphoma combined), benign tumors of the pancreas (islet-cell adenoma), and cancer of the bone (osteosarcoma) and nasal cavity (carcinoma) in males and benign mammary-gland tumors (fibroma or fibroadenoma) in females (Soffritti *et al.* 2002). Increased incidences of tumors observed at other sites occurred only at one of the lower doses tested.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to acetaldehyde. A survey of workers producing acetaldehyde and other aldehydes in Germany reported 9 cases of cancer, including 5 of lung cancer and 2 of oral-cavity cancer, among an unspecified number of workers; these incidences reportedly were higher than expected, but the observations were confounded by the fact that all cases of cancer occurred in tobacco smokers (IARC 1985, 1987).

Since acetaldehyde was listed in the *Sixth Annual Report on Carcinogens,* additional epidemiological studies have been identified, primarily case-control studies of populations exposed to acetaldehyde (the main initial metabolite of alcohol) following consumption of alcoholic beverages. Alcoholic beverage consumption is listed in the Report on Carcinogens as *known to be a human carcinogen.* In its 1999 review, the International Agency for Research on Cancer noted that three small case-control studies found increased risks of alcohol-related cancer (of the oral cavity, pharynx, larynx, and esophagus) among individuals with genetic variations (polymorphisms) that result in increased levels of acetaldehyde after alcohol consumption. However, IARC concluded that the data available were inadequate to evaluate the carcinogenicity of acetaldehyde (IARC 1999). Since then, a number of review articles and meta-analyses have summarized the results of subsequent studies that found dose-response relationships between alcohol consumption and cancer of the oral cavity, pharynx, larynx, and esophagus, and possibly the stomach and colorectum, among individuals with genetic polymorphisms that increase blood or salivary levels of acetaldehyde (Bagnardi *et al.* 2001, Zeka *et al.* 2003, Boffetta and Hashibe 2006, Baan *et al.* 2007, Boccia *et al.* 2009, Salaspuro 2009). In 2009, IARC concluded that acetaldehyde associated with alcohol consumption was carcinogenic to humans (Secretan *et al.* 2009). Few studies have been conducted on the association of these polymorphisms with cancer at other tissue sites, and the role of acetaldehyde in pancreatic, liver, bladder, or breast cancer is not clear (van Dijk *et al.* 2001, Terry *et al.* 2006, Seitz and Becker 2007, Visavanathan *et al.* 2007, Druesne-Pecollo *et al.* 2009).

Studies on Mechanisms of Carcinogenesis

Alcohol is metabolized to acetaldehyde by alcohol dehydrogenases (ADH), and acetaldehyde is metabolized to acetic acid by aldehyde dehydrogenases (ALDH). In some individuals, genetic polymorphisms in these enzymes can result in either higher rates of acetaldehyde production from alcohol or lower rates of acetaldehyde metabolism to acetic acid, resulting in higher blood acetaldehyde levels after a given level of alcohol intake than in individuals without these polymorphisms. Five ADH genes have been identified in humans, two of which have been shown to be polymorphic. The variant allele of the *ALDH2* gene, which is prevalent in Asians, encodes an enzyme that has almost no ability to detoxify acetaldehyde (IARC 1999).

Properties

Acetaldehyde is an aliphatic aldehyde that exists at room temperature as a colorless gas with a fruity, pungent odor. It is miscible with water, ether, benzene, gasoline, solvent naphtha, toluene, xylene, turpentine, and acetone. It is very flammable and is unstable in air (Akron 2009, HSDB 2009). Physical and chemical properties of acetaldehyde are listed in the following table.

Property	Information
Molecular weight	44.0[a]
Specific gravity	0.79 at 16°C/4°C[a]
Melting point	–124°C[a]
Boiling point	21°C[a]
Log K_{ow}	–0.34[b]
Water solubility	1,000 g/L at 25°C[a]
Vapor pressure	902 mm Hg at 25°C[a]
Vapor density relative to air	1.5[a]
Dissociation constant (pK_a)	13.6 at 25°C[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Acetaldehyde is used primarily as a chemical intermediate in the production of acetic acid, pyridine and pyridine bases, peracetic acid, pentaerythritol, butylene glycol, and chloral. It is also used in the synthesis of crotonaldehyde, flavor and fragrance acetals, acetaldehyde 1,1-dimethylhydrazone, acetaldehyde cyanohydrin, acetaldehyde oxime, various acetic acid esters, paraldehyde, metaldehyde (a molluscicide widely used to kill slugs and snails), polymers, and various halogenated derivatives (IARC 1985, 1999). Acetaldehyde has been used in the manufacture of aniline dyes, plastics, and synthetic rubber, to silver mirrors, and to harden gelatin fibers. It has also been used in the production of polyvinyl acetal resins, in fuel compositions, to inhibit mold growth on leather, and in the manufacture of disinfectants, pesticides, drugs, explosives, lacquers and varnishes, photographic chemicals, phenolic and urea resins, and rubber accelerators and antioxidants (EPA 1994).

Acetaldehyde is considered by the U.S. Food and Drug Administration to be generally recognized as safe for use as a flavoring agent and adjuvant (Furia and Bellanca 1975, HSDB 2009). It is an important component of food flavorings and is added to milk products, baked

goods, fruit juices, candy, desserts, and soft drinks; it is especially useful for imparting orange, apple, and butter flavors. The concentration of acetaldehyde in food generally is up to 0.047%. In 1976, about 8,600 kg (19,000 lb) of acetaldehyde was used as food additives. Acetaldehyde is also used in the manufacture of vinegar and as a fruit and fish preservative. It is approved for use in phenolic resins in molded containers for contact with non-acidic foods. Acetaldehyde is no longer registered as an active ingredient in any pesticide. When it was used as a fumigant for storage of apples and strawberries, it was exempted from a residue tolerance (IARC 1985, EPA 1994, HSDB 2009).

Production

Acetaldehyde was first produced commercially in 1916 (IARC 1985). U.S. production was 63.5 million kilograms (140 million pounds) in 1940 and 408 million kilograms (899 million pounds) in 1960. Production peaked in 1969 at 748 million kilograms (1.65 billion pounds), decreasing to 281 million kilograms (619 million pounds) in 1982. In 2009, acetaldehyde was produced by 50 manufacturers worldwide (17 in China, 12 in India, 6 in East Asia, 5 in Europe, 5 in Central and South America, 2 in Mexico, 2 in the Middle East, and 1 in the United States) (SRI 2009) and was available from 49 suppliers, including 21 U.S. suppliers (ChemSources 2009). U.S. imports of acetaldehyde increased from 1,000 kg (2,200 lb) in 1989 to 414,000 kg (913,000 lb) in 2006 (USITC 2009). U.S. exports of acetaldehyde were 19 million kilograms (42.6 million pounds) in 1989, decreasing to 1.6 million kilograms (3.5 million pounds) in 2003 and remaining near this level from 2004 through 2008 (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of acetaldehyde totaled 500 million to 1 billion pounds in 1986 and 1990 and 100 million to 500 million pounds in 1994, 1998, and 2002 (EPA 2004).

Exposure

There is high potential for exposure of the general population to acetaldehyde through ingestion, inhalation, and dermal contact and of workers through inhalation and dermal contact. The main source of exposure of the general population is through consumption of alcoholic beverages and the subsequent metabolism of alcohol to form acetaldehyde (HSDB 2009). Because acetaldehyde may form in wine and other alcoholic beverages after exposure to air (Hagemeyer 2002), alcoholic beverages (including wines, beer, and spirits) also frequently contain acetaldehyde as a volatile component (HSDB 2009).

Acetaldehyde is a product of most hydrocarbon oxidation reactions and is a normal intermediate in the respiration of most higher plants. It is found in trace amounts in many plant products, including apples, broccoli, coffee, grapefruit, grapes, lemons, mushrooms, onions, oranges, peaches, nectarines, pears, pineapples, raspberries, strawberries, cranberries, sour cherries, and mango. It has been detected in the essential oils of alfalfa, rosemary, balm, clary sage, daffodil, bitter orange, camphor, angelica, fennel, mustard, peppermint, and lychee, and in oak and tobacco leaves and cotton leaves and blossoms (IARC 1985, Burdon *et al.* 1996, Gorny *et al.* 1999, Gunes *et al.* 2002, Bonerz *et al.* 2007, Mahattanatawee *et al.* 2007). Acetaldehyde has also been detected in breast milk. Consumers may be exposed to acetaldehyde in many milk products, including all types of cheese, yogurt, and milk of varying fat content (Mistry and Hassan 1992, Barbieri *et al.* 1994, Jandal 1996, Beshkova *et al.* 1998, Van Aardt *et al.* 2001, Kondyli *et al.* 2002, Boscaini *et al.* 2003, Di Cagno *et al.* 2004, Fernandez-Garcia *et al.* 2004, Blagden and Gilliland 2005, Gadaga *et al.* 2007, Kaminarides *et al.* 2007). Acetaldehyde has also been detected in cooked beef, chicken, and fish (HSDB 2009, Yasuhara and Shibamoto 1995) and is used as a synthetic flavoring ingredient in processed foods, especially margarine (HSDB 2009).

According to EPA's Toxics Release Inventory, environmental releases of acetaldehyde have increased slightly since 1988, when 9.5 million pounds was released, 73% to air, 23% to underground injection wells, and the remainder to surface water and landfills. Since then, releases to underground injection wells have decreased, and releases to surface water have increased. In 2007, 11.4 million pounds of acetaldehyde was released from 336 facilities that processed, produced, or used the chemical; 29 facilities each released more than 100,000 lb. Of the total amount, 94% was released to air, 3.1% to underground injection wells, and 2.8% to water (TRI 2009). Acetaldehyde will volatilize rapidly from water or land, and it will leach into the ground, where it will biodegrade (HSDB 2009). Acetaldehyde is also degraded readily in soil, sewage, and natural waters by microorganisms (EPA 1987).

Acetaldehyde is a natural product of photooxidation of hydrocarbons commonly found in the atmosphere and occurs naturally as emissions from forest fires, volcanoes, and animal wastes. In the 1990s, annual emissions of acetaldehyde from all sources in the United States were estimated at 12.1 million kilograms (27 million pounds) (IPCS 1995). Burning wood produces acetaldehyde at approximately 0.7 g/kg of wood, and fireplace emissions range from 0.083 to 0.20 g/kg of wood burned (HSDB 2009). In the 1990s, annual emissions from residential burning in the United States were estimated at 5,000 metric tons (11 million pounds) (IPCS 1995). Acetaldehyde is also a combustion product of some plastics (e.g., polycarbonate) and some hard and soft polyurethane foams. It also occurs in gasoline exhaust (1.4 to 8.8 mg/m^3) and diesel exhaust (0.05 to 6.4 mg/m^3); however, very little is emitted from small engines such as lawn mowers or leaf blowers (IARC 1985, Baldauf *et al.* 2006).

Many individuals are exposed to acetaldehyde by inhalation. The highest ambient-air concentrations of acetaldehyde were reported for urban or suburban areas or near sources of combustion (HSDB 2009). In ambient air, concentrations of acetaldehyde generally averaged 5 $\mu g/m^3$. Indoor air concentrations were higher than ambient concentrations in all locations where acetaldehyde air concentrations were measured, both in the United States and in other countries (Miguel *et al.* 1995, Mukund *et al.* 1996, Brickus *et al.* 1998, MacIntosh *et al.* 2000, Possanzini *et al.* 2002, Baez *et al.* 2003, Hellen *et al.* 2004, Hodgson *et al.* 2004, Park and Ikeda 2004, Saijo *et al.* 2004, Sax *et al.* 2004, Shendell *et al.* 2004, Gilbert *et al.* 2005, Cavalcante *et al.* 2006, Ohura *et al.* 2006, Pang and Mu 2006, Sax *et al.* 2006, Hodgson *et al.* 2007, Possanzini *et al.* 2007). Acetaldehyde is also found in tobacco and marijuana cigarette smoke (1,220 µg per cigarette) and tobacco cigarettes (980 to 1,370 µg per cigarette).

In 1988–89, acetaldehyde was detected in 4 of 10 surveyed water supplies (EPA 1987). In surface water, concentrations generally are less than 0.1 µg/L, and the contribution from drinking water to human exposure is considered negligible (IPCS 1995).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 216,533 workers, including 97,770 women, potentially were exposed to acetaldehyde (NIOSH 1990). Workers potentially exposed include those involved in the manufacture or use of industrial organic chemicals, dyes, fabricated rubber, plastics, urea-formaldehyde foam insulation, fuels, drugs, explosives, varnishes, pesticides, food additives, leather goods, and mirrors (IARC 1985, EPA 1994).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of acetaldehyde on ships and barges.

Department of Transportation (DOT)

Acetaldehyde is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.
National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of acetaldehyde is subject to certain provisions for the control of volatile organic compound emissions.
Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of acetaldehyde = U001.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 200 ppm (360 mg/m^3).
Considered a highly hazardous chemical: Threshold quantity (TQ) = 2,500 lb.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – ceiling (TLV-C) = 25 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,000 ppm.
Listed as a potential occupational carcinogen.

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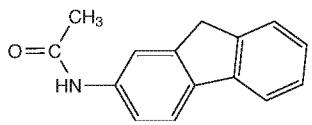
2-Acetylaminofluorene

CAS No. 53-96-3

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 2-acetamidofluorene, *N*-2-fluorenylacetamide, or *N*-fluoren-2-yl-acetamide



Carcinogenicity

2-Acetylaminofluorene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2-acetylaminofluorene caused tumors at several different tissue sites in mice and rats. Dietary administration of 2-acetylaminofluorene caused cancer of the liver (hepatocellular carcinoma) and urinary bladder (transitional-cell carcinoma) in female mice (Staffa and Mehlman 1980) and in rats of both sexes (Wilson *et al.* 1941). In rats, it also caused skin cancer (carcinoma, possibly arising from the auditory canal).

Since 2-acetylaminofluorene was listed in the *Second Annual Report on Carcinogens,* additional studies in experimental animals have been identified. In female mice, dietary administration of 2-acetylaminofluorene caused mammary-gland cancer (adenocarcinoma), as well as urinary-bladder cancer (transitional-cell carcinoma) (Greenman *et al.* 1987). In rats, dietary administration of 2-acetylaminofluorene caused liver cancer (hepatocellular carcinoma or cholangiocarcinoma) in both sexes, mammary-gland cancer (adenocarcinoma) in females, and tumors of the testes (mesothelioma of the tunica vaginalis) and Zymbal gland in males (Weisburger *et al.* 1981, Cabral and Neal 1983). A single subcutaneous injection of 2-acetylaminofluorene caused liver tumors (hepatocellular tumors) in newborn male mice (Fujii 1991). Liver tumors were also observed following dietary administration of 2-acetylaminofluorene to male dogs (Allison *et al.* 1950) and to fish of both sexes (hepatocellular tumors or cholangiocarcinoma) (Pliss and Khudoley 1975) and following addition of 2-acetylaminofluorene to the tank water of fish of unspecified sex (hepatocellular adenoma or carcinoma) (James *et al.* 1994). In hamsters of both sexes, intratracheal instillation of 2-acetylaminofluorene caused urinary-bladder cancer (transitional-cell carcinoma) (Oyasu *et al.* 1973). Intraperitoneal injection of 2-acetylaminofluorene in newborn hamsters until weaning, followed by dietary administration, caused cancer of the urinary bladder (carcinoma) and liver (cholangiocarcinoma) and benign stomach tumors (squamous-cell papilloma) (Oyasu *et al.* 1972, Matsumoto *et al.* 1976).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2-acetylaminofluorene.

Properties

2-Acetylaminofluorene is an aromatic amine that occurs as a tan crystalline powder at room temperature (Akron 2009). It is practically insoluble in water, but is soluble in glycols, alcohols, ether, acetic acid, and fat solvents (HSDB 2009). 2-Acetylaminofluorene is stable at normal temperatures and pressures, but when heated to decomposition, it produces irritating or toxic gases (e.g., nitrogen oxides, carbon monoxide, carbon dioxide, hydrogen fluoride) (Akron 2009). Physical and chemical properties of 2-acetylaminofluorene are listed in the following table.

Property	Information
Molecular weight	223.3[a]
Density	1.27 g/cm^3[b]
Melting point	194°C[a]
Boiling point	303°C[c]
Log K_{ow}	3.22[a]
Water solubility	144 mg/L at 25°C[a]
Vapor pressure	9.44×10^{-8} mm Hg at 25°C[c]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

2-Acetylaminofluorene is used as a research tool, primarily as a positive control in studies of the carcinogenicity and mutagenicity of other chemicals (HSDB 2009). 2-Acetylaminofluorene was intended for use as a pesticide, but it was never marketed, because of its carcinogenicity in experimental animals.

Production

2-Acetylaminofluorene is not currently produced in commercial quantities in the United States or anywhere else in the world (SRI 2009). One U.S. producer of 2-acetylaminofluorene was reported in 1977, but production volume was not reported (TSCA 1979). In 2009, 2-acetylaminofluorene was distributed by 17 specialty chemical companies, including 11 in the United States (ChemSources 2009). These distributors typically sell 2-acetylaminofluorene in small quantities, and total estimated U.S. usage is low.

Exposure

The routes of potential human exposure to 2-acetylaminofluorene are inhalation, ingestion, and dermal contact (HSDB 2009). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of 2-acetylaminofluorene increased from 9,800 lb in 1998 to 81,000 lb in 2001, declined to a low of 255 lb in 2003, and have remained below 1,000 lb since 2003. Most of the releases were to hazardous-waste landfills. In 2007, one facility released about 500 lb of 2-acetylaminofluorene to a hazardous-waste landfill and about 250 lb to air (TRI 2009). The risk of occupational exposure to 2-acetylaminofluorene is greatest for chemists, chemical stockroom workers, and biomedical researchers. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 373 workers potentially were exposed to 2-acetylaminofluorene (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 2-acetylaminofluorene = U005.

Listed as a hazardous constituent of waste.

Mine Safety and Health Administration

To control airborne exposure, 2-acetylaminofluorene shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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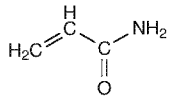
Acrylamide

CAS No. 79-06-1

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as 2-propenamide



Carcinogenicity

Acrylamide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Acrylamide caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Administration of acrylamide in the drinking water caused benign thyroid-gland tumors (follicular-cell adenoma) in rats of both sexes. In male rats, it also caused tumors of the lining of the testes (mesothelioma of the tunica albuginea) and benign adrenal-gland tumors (pheochromocytoma). In female rats, it also caused cancer of the uterus (adenocarcinoma), benign and malignant tumors of the mammary gland (adenoma and adenocarcinoma), and benign tumors of the pituitary gland (adenoma), oral cavity (papilloma), and clitoral gland (ade-

noma). In strain A/J mice (a strain with a high spontaneous incidence of lung cancer), administration of acrylamide by stomach tube or by intraperitoneal injection increased both the incidence of benign lung tumors (adenoma) and number of tumors per animal in both sexes. In initiation-promotion studies, acrylamide administered dermally, by stomach tube, or by intraperitoneal injection followed by long-term dermal exposure to the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate induced benign and malignant skin tumors (squamous-cell papilloma and carcinoma) in female mice (IARC 1986).

Cancer Studies in Humans

Most of the available epidemiological studies of cancer and exposure to acrylamide have been published since acrylamide was listed in the *Sixth Annual Report on Carcinogens.* In a study of a multi-plant cohort consisting mostly of male workers, the incidence of pancreatic cancer was significantly higher among workers with the highest cumulative exposure to acrylamide than in the U.S. population. Among exposed workers, the incidence of pancreatic cancer was significantly associated with duration of exposure and time since first exposure (Marsh *et al.* 1999, Schulz *et al.* 2001). In a follow-up of this cohort, the relative risk of pancreatic cancer increased with increasing duration of exposure after adjustment for smoking, but the trend was not statistically significant, and no clear trends were observed for cumulative or average exposure (Marsh *et al.* 2007). A small cohort study of U.S. workers (mostly male) found statistically nonsignificant increases in the risks for cancers of the digestive system, including pancreatic cancer (Sobel *et al.* 1986, Swaen *et al.* 2007).

Several population-based studies that investigated the association between dietary intake of acrylamide and specific cancer outcomes were reviewed by Hogervorst *et al.* (2010). Several prospective cohort studies used case-cohort or nested case-control analyses to evaluate dietary exposure to acrylamide (based on a food-frequency questionnaire) and the risks of cancer at specific tissue sites; these include the Swedish Women's Lifestyle and Health Cohort, the Swedish Mammography Cohort, the Netherlands Study on Diet and Cancer, a cohort of Swedish men, the U.S. Nurses' Health Study, and the Danish Diet, Cancer, and Health Study. In addition, several case-control studies (most of which used food-frequency questionnaires) assessed cancer and dietary exposure of Swedish, French, and U.S. populations to acrylamide. The tissue site studied most frequently was the breast. These studies found no overall association between breast cancer and dietary exposure to acrylamide; however, some, but not all, studies reported an association between acrylamide exposure and a specific type of breast cancer (sex-hormone-receptor-positive cancer in post-menopausal women). The Danish study used acrylamide-hemoglobin adducts to assess exposure; however, these adducts are not source-specific, but reflect both dietary exposure and exposure from other sources, such as smoking. Two of three prospective cohort studies reported increased risks of endometrial and ovarian cancer, but a case-control study found no increased risk of ovarian cancer. Most of the studies evaluating prostate and colorectal cancer did not find increased risks associated with dietary exposure to acrylamide. Findings were mixed for cancer of the kidney, head, and neck, and evaluation of cancer at other tissue sites was limited by the small numbers of studies.

Properties

Acrylamide is an unsaturated amide that exists as a white, odorless crystalline solid at room temperature. It is soluble in water, methanol, ethanol, acetone, ethyl acetate, and chloroform, and insoluble in benzene and heptane. Acrylamide is stable under normal conditions but may decompose or polymerize when heated or exposed to ultraviolet light (Akron 2009). When heated to decomposition, acrylamide emits acrid fumes and nitrogen oxides (HSDB 2009). Commercial acrylamide monomer contains residual levels of acrylonitrile (1 to 100 mg/kg) (IARC 1986). Residual acrylamide monomer is present in the polymer at approximately 0.01% (Fujiki *et al.* 1984, IARC 1986). Physical and chemical properties of acrylamide are listed in the following table.

Property	Information
Molecular weight	71.1
Specific gravity	1.122 at 30°C/4°C
Melting point	84.5°C
Boiling point	192.6°C
Log K_{ow}	–0.67
Water solubility	371 g/L at 20°C
Vapor pressure	7×10^{-3} mm Hg at 25°C
Vapor density relative to air	2.5

Source: HSDB 2009.

Use

Acrylamide is a chemical intermediate used in the production and synthesis of polyacrylamides that can be modified to develop nonionic, anionic, or cationic properties for specific uses. These water-soluble polymers can be used as additives for water treatment, enhanced oil recovery, flocculants, papermaking aids, thickeners, soil-conditioning agents, sewage and waste treatment, ore processing, and permanent-press fabrics (Habermann 2002). In 2001, 94% of acrylamide was used to produce polyacrylamide, of which 56% was used for water treatment, 24% for pulp and paper production, 10% for mineral processing, 4% for miscellaneous uses, and the remaining 6% for production of *N*-methylolacrylamide and other monomers (CMR 2002). Acrylamide is also used in the synthesis of dyes, in copolymers for contact lenses, and in the construction of dam foundations, tunnels, and sewers (Habermann 2002).

The U.S. Food and Drug Administration has regulated the use of acrylamide and polyacrylamide in foods (IARC 1994). Acrylamide polymers containing less than 0.2% monomer may be used in food-packaging adhesives, paper, and paperboard; to wash or peel fruits and vegetables; and in gelatin capsules. In acrylamide polymers added to water for steam that will contact food, the monomer should not exceed 0.05% by weight.

Production

In 2002, four U.S. producers of acrylamide reported a production capacity of 301 million pounds (CMR 2002). In 2009, acrylamide was produced by 30 manufacturers worldwide, including 4 in the United States (SRI 2009), and was available from 55 suppliers, including 28 U.S. suppliers (ChemSources 2009). The demand for acrylamide increased from 191 million pounds in 2000 to 200 million pounds in 2001 (CMR 2002). In 1972, U.S. imports of acrylamide were considered negligible (HSDB 2009). Imports totaled 6.8 million kilograms (15 million pounds) in 1992, 2 million pounds in 2001, 2.9 million kilograms (6.4 million pounds) in 2007, and 2.6 million kilograms (5.8 million pounds) in 2008. U.S. exports of acrylamide were less than 0.9 million kilograms (2 million pounds) in 1992, 11 million pounds in 2000, and 8 million pounds in 2001; no more recent data on exports were found (EPA 1994, CMR 2002, USITC 2009). Reports filed from 1988 to 2006 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of acrylamide totaled 100 million to 500 million pounds except in 1990, when the quantity was 50 million to 100 million pounds (EPA 2004, 2009).

Exposure

The potential routes of human exposure to acrylamide are ingestion, dermal contact, and inhalation (Manson *et al.* 2005). Acrylamide has been found in a number of food products. In 2002, a Swedish study reported that acrylamide was formed in heated foodstuffs, especially potato products and other baked or fried high-carbohydrate foodstuffs (Tareke *et al.* 2002). The acrylamide content of food items is directly related to the amount of reducing sugars and asparagine in the raw product and the cooking temperature used in the preparation (Pedreschi *et al.* 2004). Studies have quantified acrylamide content in foods such as potato chips (up to 3,700 µg/kg), French fries (up to 12,000 µg/kg), cereal (up to 1,346 µg/kg), bread (biscuits and crackers, up to 3,200 µg/kg), gingerbread (up to 1,660 µg/kg), nuts and nut butters (up to 457 µg/kg), and coffee (up to 16 µg/L) (Friedman 2003, Andrzejewski *et al.* 2004, Hoenicke *et al.* 2004, Aguas *et al.* 2006). Average U.S. daily dietary intake for all individuals over the age of two years was estimated at 0.43 µg/kg of body weight; however, the estimated exposure of children aged two to five years was 1.06 µg/kg (Manson *et al.* 2005).

Acrylamide may also be ingested in drinking water contaminated by polyacrylamide flocculants used in water treatment (Brown *et al.* 1980a, Howard 1989). Residual acrylamide concentrations in 32 polyacrylamide flocculants approved for water-treatment plants ranged from 0.5 to 600 ppm (Howard 1989). Acrylamide remains in water after flocculation with polyacrylamides because it is very water soluble and is not readily adsorbed by sediment (Brown *et al.* 1980b, Howard 1989).

Dermal exposure to acrylamide may result from trace quantities in cosmetic products, gardening products, paper and pulp products, coatings, and textiles resulting from the use of polyacrylamide in these products (Manson *et al.* 2005). Acrylamide has been measured in body and hand lotions, powders, and creams at concentrations of up to 1,200 µg/kg, and daily exposure to acrylamide through cosmetic products was estimated at 0.95 µg/kg of body weight per day. Acrylamide also has been measured in mainstream cigarette smoke at concentrations of up to 2.34 µg per cigarette, which would result in an average daily intake of 0.67 µg/kg of body weight per day (based on a body weight of 70 kg) for a person smoking one pack a day.

Acrylamide may be released into the environment in waste from acrylamide production and the manufacture of polyacrylamides and other polymers (Howard 1989). The most important environmental contamination results from the use of acrylamide in soil grouting (IPCS 1985). Acrylamide is also released to water from acrylamide-based sewer grouting and wastepaper recycling (Brown *et al.* 1980a, 1982, Howard 1989). In 2005, EPA's Toxics Release Inventory reported environmental releases of 8,797,482 lb of acrylamide from 42 facilities, 99.9% of which was released to underground injection wells, and most of the rest to air (TRI 2009).

Because the vapor pressure of acrylamide is low, the monomer is not expected to occur in the vapor phase in air. Acrylamide biodegrades in surface water in approximately 8 to 12 days (Howard 1989). Acrylamide degradation in a secondary sewage plant would be complete in approximately 10 days; however, acrylamide has been detected in effluent from sewage treatment plants (HSDB 2009). Certain debris organisms that exist in anaerobic, light aerobic, or dark aerobic conditions in natural and polluted environments are able to degrade acrylamide (Brown *et al.* 1980b). Acrylamide is highly mobile in aqueous environments; it thus readily leaches into soil and is carried great distances in groundwater of deep rock aquifers, where it will not be biodegraded (IPCS 1985). Bioconcentration of acrylamide is unlikely, because it degrades easily in surface waters and is highly water soluble (Manson *et al.* 2005). In an EPA study of five industrial sites of acrylamide and polyacrylamide production and one site of polyacrylamide use, the highest concentration of acrylamide in water was found downstream from a polyacrylamide producer, at 1.5 mg/L (IPCS 1985, Howard 1989). In this study, the average acrylamide concentration was less than 0.2 µg/m^3 in air and less than 0.02 mg/kg in soil and sediment (IPCS 1985).

Occupational exposure to acrylamide is primarily from dermal contact with the solid monomer and inhalation of dust and vapor during acrylamide and polyacrylamide production. The highest exposure occurs during the handling of the monomer. In two acrylamide manufacturing plants, breathing-zone concentrations were 0.1 to 3.6 mg/m^3. During normal operations, workers at another plant were exposed to concentrations of up to 0.3 mg/m^3 (IARC 1986). At U.S. acrylamide production facilities, the mean concentration of acrylamide in air was 640 µg/m^3 in packing areas (Manson *et al.* 2005). In other parts of the world, acrylamide-hemoglobin adducts were used to estimate occupational exposure. In China, the highest acrylamide adduct concentration was 34,000 pmol/g of globin, found in the blood of workers in an acrylamide and polyacrylamide manufacturing plant. Occupationally exposed German smokers had adduct concentrations of up to 85 pmol/g of hemoglobin. In tunnel workers exposed to polyacrylamide in grout, acrylamide adducts were found at concentrations of up to almost 17,000 pmol/g (IARC 1986). Occupational exposure to acrylamide in aqueous form occurs mainly during maintenance and repair operations and connection and disconnection of equipment for transport. Routine exposure is minimal in captive production operations (Klaassen 1986). Improvements in the polymerization process have reduced the monomer content of the nonpotable-water-grade polymers from 5% to 0.3% (Brown *et al.* 1982).

Workers in the paper and pulp, construction, foundry, oil-drilling, textiles, cosmetics, food-processing, plastics, mining, and agricultural industries also are potentially exposed to acrylamide (Manson 2005). The potential for exposure is higher among grouters than other workers, because of the uncontrolled nature of the exposure; however, exposure levels have not been reported for grouters (IPCS 1985). The National Institute for Occupational Safety and Health estimated in 1976 that about 20,000 workers potentially were exposed to acrylamide (IARC 1986), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 10,651 workers potentially were exposed (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of acrylamide solution on ships and barges.

Department of Transportation (DOT)

Acrylamide is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of acrylamide is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.
Reportable quantity (RQ) = 5,000 lb.
Threshold planning quantity (TPQ) = 1,000 lb for solids in powder form with particle size < 100 µm or solution or molten form; = 10,000 lb for all other forms.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of acrylamide = U007, K014.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Each public water system must certify annually that when acrylamide is used in drinking-water systems, the level does not exceed 0.05% dosed at 1 mg/L (or equivalent).

Food and Drug Administration (FDA)

Acrylamide and various acrylamide copolymers may be used as food additives permitted for direct addition to food for human consumption, indirect food additives, secondary direct food additives, and food additives permitted in feed and drinking water of animals, as prescribed in 21 CFR parts 172, 173, 175, 176, 177, 178, and 573.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 0.3 mg/m^3.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted-average (TLV-TWA) = 0.03 mg/m^3.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.03 mg/m^3.
Immediately dangerous to life and health (IDLH) limit = 60 mg/m^3.
Listed as a potential occupational carcinogen.

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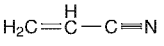
Acrylonitrile

CAS No. 107-13-1

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Acrylonitrile is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Acrylonitrile caused tumors at several different tissue sites in rats. Exposure to acrylonitrile in drinking water or by inhalation caused cancer of the central nervous system (microglioma or glioma) and Zymbal gland (carcinoma) and benign tumors of the forestomach (squamous-cell papilloma or acanthoma) in both sexes (IARC 1979).

Since acrylonitrile was listed in the *Second Annual Report on Carcinogens,* additional studies in rodents have been identified. Oral exposure to acrylonitrile caused cancer of the forestomach (squamous-cell carcinoma) and increased the combined incidence of benign and malignant Harderian-gland tumors (adenoma and carcinoma) in mice of both sexes. Benign and malignant tumors of the ovary (granulosa-cell tumors) and lung (alveolar/bronchiolar adenoma and carcinoma) in female mice also may have been related to acrylonitrile exposure (NTP 2001). In rats, prenatal exposure followed by postnatal inhalation exposure to acrylonitrile caused brain tumors

(glial-cell tumors) in both sexes. In females, it also caused cancer of the mammary gland and the blood vessels (angiosarcoma); in males, it caused cancer of the Zymbal gland and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) (IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to acrylonitrile. An increased risk of cancer of the lung and colon was reported in U.S. textile plant workers exposed to acrylonitrile and observed for 20 years or more (IARC 1979).

Since acrylonitrile was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified. In studies of workers exposed to acrylonitrile (including textile workers and rubber workers) published in the 1980s and 1990s, including several meta-analyses, the risk of cancer was increased only for lung cancer among workers with the highest cumulative exposure levels in a large National Cancer Institute cohort study (IARC 1999). An update of a U.S. textile-worker cohort followed for five decades found no association betweeen acrylonitrile exposure and cancer at any tissue site (Symons *et al.* 2008). A large international case-control study of lung cancer found a significant smoking-adjusted risk of lung cancer with increasing acrylonitrile exposure (Scélo *et al.* 2004), and a meta-analysis of lung-cancer findings found increased risk with acrylonitrile exposure after adjusting for a healthy-worker effect (Sponsiello-Wang *et al.* 2006). A small cohort study (Czeizel *et al.* 2004) found no excesses of lung or other cancer among workers possibly exposed to acrylonitrile; however, the study's statistical power to detect effects was limited. In an update of a cohort study in the Netherlands, excesses of brain cancer were found in some exposure categories (Swaen *et al.* 2004).

Properties

Acrylonitrile exists at room temperature as a volatile, flammable colorless liquid with a sweet characteristic odor. It is soluble in water and isopropyl alcohol and miscible with ethanol, carbon tetrachloride, ethyl acetate, ethylene cyanohydrin, xylene, toluene, petroleum ether, and liquid carbon dioxide. Acrylonitrile is stable under normal shipping and handling conditions but may undergo explosive polymerization if not inhibited (Akron 2009). Physical and chemical properties of acrylonitrile are listed in the following table.

Property	Information
Molecular weight	53.1
Specific gravity	0.8004 at 25°C/4°C
Melting point	–82°C
Boiling point	77.3°C at 760 mm Hg
Log K_{ow}	0.25
Water solubility	74.5 g/L at 25°C
Vapor pressure	109 mm Hg at 25°C
Vapor density relative to air	1.8

Source: HSDB 2009.

Use

Acrylonitrile is an important industrial chemical used extensively in the manufacture of synthetic fibers, resins, plastics, elastomers, and rubber for a variety of consumer goods, such as textiles, drinking cups, automotive parts, and appliances (Brazdil 2010). It is also used as a monomer for acrylic and modacrylic fibers, in plastics, in surface coatings, as a chemical intermediate, in organic synthesis, in home furnishings, in nitrile rubbers, and as a modifier for natural polymers (HSDB 2009). Of total acrylonitrile production, reported uses were 38% for the production of adiponitrile, 22% for acrylonitrile-butadiene-styrene and styrene-acrylonitrile resins, 17% for acrylic fibers, 11% for acrylamide, 3% for nitrile elastomers, and 9% for miscellaneous uses, including polymers, polyols, barrier resins, and carbon fibers (CEN 2009). Acrylonitrile is used in the manufacture of carbon fibers used to reinforce composites for high-performance applications in the aircraft, defense, and aerospace industries. Other specialty applications include the production of fatty amines, ion-exchange resins, and fatty amine amides used in cosmetics, adhesives, corrosion inhibitors, and water-treatment resins (IARC 1999). Acrylonitrile was formerly used as a fumigant; however, almost all pesticide registrations for acrylonitrile were canceled in 1978 (ATSDR 1990).

Production

Acrylonitrile has been produced in the United States since 1940 (IARC 1979). It was ranked among the 50 highest-volume chemicals for several years (CEN 2009). U.S. production of acrylonitrile averaged 2.7 billion pounds from 1985 to 1987 and totaled 2.7 billion pounds in 1990 and 2.5 billion pounds in 1993. Production increased to 3.4 billion pounds in 1996 (IARC 1999), but had decreased to 2.2 billion pounds by 2008 (CEN 2009). In 2009, acrylonitrile was produced by 32 companies worldwide, including 5 in the United States (SRI 2009), and was available from 16 U.S. suppliers (ChemSources 2009). In 2000, U.S. imports of acrylonitrile exceeded 17 million pounds; since then, imports have decreased and have varied widely, from a low of 26,000 lb in 2004 to a high of 1.1 million pounds in 2008. U.S. exports of acrylonitrile exceeded 1.5 billion pounds in 2000 and reached a high of almost 3 billion pounds in 2004 (USITC 2009).

Exposure

The potential routes of human exposure to acrylonitrile are inhalation, ingestion, and dermal contact. Exposure is greater in occupational settings than in the general population. The general population may be exposed through the use of consumer products made with polymers of acrylonitrile, such as acrylic carpeting or polyacrylonitrile-resin-based food packaging. However, exposure from these sources is very low, because little of the monomer migrates from such products into air or food (ATSDR 1990). The U.S. Consumer Product Safety Commission in 1978 estimated concentrations of acrylonitrile as less than 1 ppm in acrylic and modacrylic fibers, 30 to 50 ppm in acetonitrile-butadiene-styrene copolymers, 15 ppm in styrene-acrylonitrile copolymers, and 0 to 750 ppm in nitrile rubber and latex goods (as cited in IPCS 1983). Foods most likely to contain measureable acrylonitrile are high-fat or highly acidic items, such as luncheon meat, peanut butter, margarine, vegetable oil, or fruit juice. In 1984, typical concentrations of acrylonitrile in margarine were reported to be 25 μg/kg (ATSDR 1990). However, the U.S. Food and Drug Administration's Total Diet Study found no acrylonitrile residue in any of the foods tested from 1991 to 2004 (FDA 2006).

Acrylonitrile has been measured in the vapor phase of mainstream tobacco smoke at a concentration of 18.5 μg per cigarette (Laugesen and Fowles 2005). Indoor air concentrations of acrylonitrile in the residences of smokers (to which nonsmokers were exposed) were estimated at 0.5 to 1.2 μg/m^3 (Nazaroff and Singer 2004). Acrylonitrile-hemoglobin adducts are a reliable marker of smoking behavior and correlate with the number of cigarettes smoked per day (Bergmark 1997, Fennell *et al.* 2000). The adducts may also be present in infants born to mothers who smoke (Tavares *et al.* 1996, Schettgen *et al.* 2004).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, the volume of environmental releases of acrylo-

nitrile has remained high since 2001, when 11.5 million pounds was released, and most releases since 2000 have been to underground injection wells. In 2007, 94 facilities released a total of about 7 million pounds of acrylonitrile, most of which (6.6 million pounds) was released by two facilities to on-site hazardous waste underground injection wells (TRI 2009).

Occupational exposure to acrylonitrile may occur during its manufacture and production and in factories where it is used as a monomer; exposure levels are highest where acrylonitrile is manufactured. Typical workplace air concentrations were reported to range from 0.1 to 4 mg/m^3 (ATSDR 1990). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 51,153 workers, including 25,320 women, potentially were exposed to acrylonitrile. Occupations with potential for exposure included acrylic resin, rubber, synthetic fiber, and textile maker; synthetic organic chemist; and pesticide worker (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of acrylonitrile on ships and barges.

Department of Transportation (DOT)

Acrylonitrile is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of acrylonitrile is subject to certain provisions for the control of volatile organic compound emissions.
Prevention of Accidental Release: Threshold quantity (TQ) = 20,000 lb.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.
Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.051 µg/L; based on fish or shellfish consumption only = 0.25 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.
Reportable quantity (RQ) = 100 lb.
Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of acrylonitrile = U009, K011, K013.
Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Acrylonitrile copolymers and resins may be used in materials that are intended for use in producing, manufacturing, processing, preparing, treating, packaging, transporting, or holding food, as prescribed in 21 CFR parts 173, 175, 176, 177, 178, 179, 180, 181.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Ceiling concentration = 10 ppm (15-min exposure).
Permissible exposure limit (PEL) = 2 ppm.
Comprehensive standards for occupational exposure to acrylonitrile have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 10 ppm (15-min exposure).
Immediately dangerous to life and health (IDLH) limit = 85 ppm.
Recommended exposure limit (time-weighted-average workday) = 1 ppm.
Listed as a potential occupational carcinogen.

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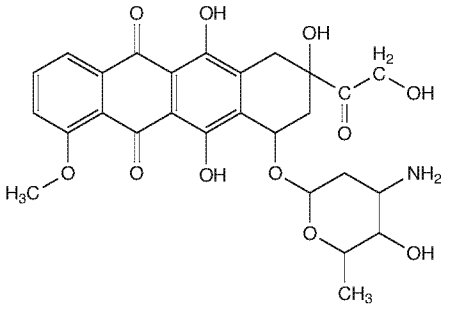
Adriamycin

CAS No. 23214-92-8

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Adriamycin is a registered trademark of Pharmacia Company for doxorubicin hydrochloride (CAS No. 25136-40-9)



Carcinogenicity

Adriamycin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Adriamycin caused tumors in rats at several different tissue sites and by several different routes of exposure. A single intravenous injection of Adriamycin caused mammary-gland tumors in female rats in several studies. In rats of unspecified sex, single or repeated subcutaneous injections of Adriamycin caused cancer of the mammary gland and at the injection site (sarcoma) (IARC 1976, 1982).

Since Adriamycin was listed in the *Fourth Annual Report on Carcinogens,* additional studies in experimental animals have been identified. In rats of unspecified sex, instillation of Adriamycin into the urinary bladder resulted in a low incidence of benign urinary-bladder tumors (papilloma) and promoted the induction of urinary-bladder tumors by *N*-nitroso-*N*-(4-hydroxybutyl)-*N*-butylamine (IARC 1982, 1987). When Adriamycin was administered to rhesus and cynomolgus monkeys by intravenous injection, a single malignant tumor (fibrosarcoma) was observed at the injection site in one cynomolgus monkey (Thorgeirsson *et al.* 1994, Schoeffner and Thorgeirsson 2000).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to Adriamycin. However, some cancer patients who received Adriamycin in combination with alkylating agents and radiotherapy developed acute nonlymphocytic leukemia and bone tumors (osteosarcoma) (IARC 1982).

Properties

Adriamycin is an anthracycline antibiotic that is an almost odorless red crystalline solid. It is soluble in water and aqueous alcohols, moderately soluble in anhydrous methanol, and insoluble in nonpolar organic solvents (IARC 1976). It is stable at room temperature in closed containers under normal storage conditions (Akron 2009). Physical and chemical properties of Adriamycin are listed in the following table.

Property	Information
Molecular weight	543.5[a]
Melting point	229°C to 231°C[b]
Log K_{ow}	1.27 at pH 7.4[a]
Water solubility	20 g/L[a]
Vapor pressure	8.99×10^{-25} mm Hg[b]
Dissociation constant (pK_a)	8.33[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Adriamycin is a cytotoxic anthracycline antibiotic used in antimitotic chemotherapy. It is infused intravenously to treat neoplastic diseases such as acute leukemia, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, soft-tissue and osteogenic sarcomas, Kaposi's sarcoma, neuroblastoma, Ewing's sarcoma, Wilms' tumor, and cancer (carcinoma) of the head and neck, breast, thyroid gland, genitourinary tract, and lung (IARC 1976, Chabner *et al.* 2001, HSDB 2009, MedlinePlus 2009). A liposomal doxorubicin product is available to treat AIDS-related Kaposi's sarcoma.

Production

In 2009, Adriamycin was produced by four manufacturers worldwide (two in Europe and one each in China and East Asia) (SRI 2009); doxorubicin hydrochloride was available from eight U.S. suppliers (ChemSources 2009), and five pharmaceutical companies produced 15 injectable pharmaceutical products approved by the U.S. Food and Drug Administration containing doxorubicin hydrochloride (FDA 2009). No data were found on U.S. imports or exports of Adriamycin.

Exposure

The primary source of human exposure is by intravenous injection of patients treated with Adriamycin. When Adriamycin is used as a single agent for treatment of adult patients, the most common dosage schedule is 60 to 75 mg/m^2 of body surface as a single intravenous infusion over 30 minutes at 21-day intervals until a total of 550 mg/m^2 is given (IARC 1976). The liposomal product is also administered intravenously at 21-day intervals at a dose of 20 mg/m^2 (Chabner *et al.* 2001). In 2009, 378 clinical trials with regimens including Adriamycin were in progress or recently completed (ClinicalTrials 2009). Healthcare professionals and support staff (including custodians) may be exposed to Adriamycin by dermal contact, inhalation, or accidental ingestion during drug preparation and administration or cleanup of medical waste, including excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). Adriamycin can be found unchanged in human excrement (RxMed 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 17,132 health-services workers, including 11,918 women, potentially were exposed to Adriamycin (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Adriamycin is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Aflatoxins

CAS No. 1402-68-2

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Aflatoxins are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans. Aflatoxins were listed in the *First Annual Report on Carcinogens* as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals and limited evidence of carcinogenicity from studies in humans; however, the listing was revised to *known to be human carcinogens* in the *Sixth Annual Report on Carcinogens* in 1991.

Cancer Studies in Humans

Early evidence for the carcinogenicity of aflatoxins in humans came from epidemiological studies (a case-control study and descriptive studies) that correlated geographic variation in aflatoxin content of foods with geographic variation in the incidence of liver cancer (hepatocellular carcinoma, or primary liver-cell cancer). Studies in Uganda, Swaziland, Thailand, Kenya, Mozambique, and China demonstrated strong, significant positive correlations between estimated aflatoxin intake or aflatoxin levels in food samples and the incidence of liver cancer. In the United States, a 10% excess of primary liver-cell cancer was observed in the Southeast, where the estimated average daily intake of aflatoxin was high, compared with the North and West, areas with low aflatoxin intake. In a case-control study in the Philippines, levels of aflatoxin in the diets of individuals were estimated retrospectively, and the risk of liver cancer increased significantly with increasing estimated aflatoxin consumption. Interpretation of these studies is complicated by potential confounding due to hepatitis B virus infection, which is endemic in many of the study areas and is known to cause primary liver-cell cancer (IARC 1987, 1993).

In studies that took into account the prevalence of chronic hepatitis B infection, aflatoxin exposure remained strongly associated with liver cancer. Chinese studies in which the prevalence of chronic hepatitis B did not appear to fully explain differences in rates of primary liver-cell cancer were reviewed, and it was concluded that the remaining variance in liver-cancer incidence was related both to estimated dietary levels of aflatoxins and to measured levels of aflatoxins and their metabolites in the urine. In a study in Swaziland, estimated aflatoxin intake based on levels in food samples was strongly correlated with liver-cancer incidence; in this study, geographic variation in aflatoxin exposure better explained the variation in liver-cancer incidence than did variation in the prevalence of hepatitis B infection (IARC 1987, 1993).

The International Agency for Research on Cancer concluded in 1987 that there was sufficient evidence in humans for the carcinogenicity of naturally occurring aflatoxins (IARC 1987). This conclusion was reaffirmed in two subsequent reevaluations (IARC 1993, 2002). These reevaluations considered the results of several cohort studies in China and Taiwan, which reported associations between biomarkers for aflatoxin exposure (aflatoxin metabolites in the urine and aflatoxin-albumin adducts in the blood) and primary liver-cell cancer; the association remained when the analyses controlled for hepatitis B infection.

Studies on Mechanisms of Carcinogenesis

Aflatoxin causes genetic damage in bacteria, in cultured cells from humans and experimental animals, and in humans and experimental animals exposed to aflatoxin *in vivo*. Types of genetic damage observed include formation of DNA and albumin adducts, gene mutations, micronucleus formation, sister chromatid exchange, and mitotic recombination. Metabolically activated aflatoxin B_1 specifically induced G to T transversion mutations in bacteria. G to T transversions in codon 249 of the *p53* tumor-suppressor gene have been found in human liver tumors from geographic areas with high risk of aflatoxin exposure and in experimental animals (IARC 1993, 2002).

In humans and susceptible animal species, aflatoxin B_1 is metabolized by cytochrome P450 enzymes to aflatoxin-8,9-epoxide, a reactive form that binds to DNA and to albumin in the blood serum, forming adducts. Comparable levels of the major aflatoxin B_1 adducts (the N^7-guanine and serum albumin adducts) have been detected in humans and susceptible animal species. The 8,9-epoxide metabolite can be detoxified through conjugation with glutathione, mediated by the enzyme glutathione S-transferase (GST). The activity of GST is much higher (by a factor of 3 to 5) in animal species that are resistant to aflatoxin carcinogenicity, such as mice, than in susceptible animal species, such as rats. Humans have lower GST activity than either mice or rats, suggesting that humans are less capable of detoxifying aflatoxin-8,9-epoxide. In studies of rats and trout, treatment

with chemopreventive agents reduced the formation of aflatoxin B_1–guanine adducts and the incidence of liver tumors.

Cancer Studies in Experimental Animals

Aflatoxins caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Oral administration of aflatoxin mixtures or aflatoxin B_1 alone (in the diet, by stomach tube, or in the drinking water) caused liver tumors (hepatocellular or cholangiocellular tumors) in all species tested except mice; these included rats, hamsters, marmosets, tree shrews, and monkeys. In addition, kidney (renal-cell) and colon tumors occurred in rats, benign lung tumors (adenoma) in mice, and tumors of the liver, bone (osteogenic sarcoma), gallbladder, and pancreas (adenocarcinoma) in monkeys. When administered by intraperitoneal injection, aflatoxin B_1 caused liver tumors in infant mice, adult rats, and toads. Aflatoxin B_1 administered by intraperitoneal injection to pregnant and lactating rats caused tumors of the liver, digestive tract, urogenital system, and nervous system in the mothers and offspring. Aflatoxin mixtures administered by subcutaneous injection caused tumors at the injection site (sarcoma) in rats and mice. Aflatoxins B_2, G_1, and M_1 also caused liver tumors in experimental animals, but generally at lower incidences than did aflatoxin mixtures or aflatoxin B_1 alone. In rats, aflatoxin G_1 also caused kidney tumors when administered orally and a low incidence of injection-site tumors (sarcoma) when administered by intraperitoneal injection. Both enhancement and inhibition of aflatoxin's carcinogenicity were observed following co-administration of aflatoxins with various diets, viruses, parasites, known carcinogens, and other chemicals (IARC 1976, 1993).

IARC (1993) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of naturally occurring mixtures of aflatoxins and aflatoxins B_1, G_1, and M_1; limited evidence for the carcinogenicity of aflatoxin B_2; and inadequate evidence for the carcinogenicity of aflatoxin G_2. In its 2002 evaluation, IARC reported on several more recent studies suggesting that experimental animals infected with hepatitis B virus (woodchucks, tree shrews, and transgenic mice heterozygous for the *p53* tumor-suppressor gene) were more sensitive to the carcinogenic effects of aflatoxin than were uninfected animals. IARC (2002) concluded that these studies confirmed the carcinogenicity of aflatoxins in experimental animals.

Properties

Aflatoxins are toxins produced by fungi in the genus *Aspergillus* that grow on grains and other agricultural crops. They exist as colorless to pale-yellow crystals at room temperature (IARC 1976, 1993). They are slightly soluble in water and hydrocarbons, soluble in methanol, acetone, and chloroform, and insoluble in nonpolar solvents. Aflatoxins are relatively unstable in light and air, particularly in polar solvents or when exposed to oxidizing agents, ultraviolet light, or solutions with a pH below 3 or above 10. Aflatoxins decompose at their melting points, which are between 237°C (G_1) and 299°C (M_1), but are not destroyed under normal cooking conditions. They can be completely destroyed by autoclaving in the presence of ammonia or by treatment with bleach. Physical and chemical properties of aflatoxins are listed in the following table.

Property	Information
Melting point	237°C to 299°C[a]
Log K_{ow}	0.5[b]
Water solubility	3.150 g/L at 25°C[b]
Vapor pressure	1.25×10^{-10} mm Hg at 25°C[b]

Sources: [a]IARC 1993, [b]ChemIDplus 2009.

The four major types of aflatoxins are designated aflatoxin B_1 (molecular weight = 312.3), B_2 (molecular weight = 314.3), G_1 (molecular weight = 328.3), and G_2 (molecular weight = 330.3), based on their fluorescent color when exposed to ultraviolet light (B = blue fluorescence, G = yellow-green fluorescence). Aflatoxin M_1, which may be found in the absence of other aflatoxins, is a major metabolic hydroxylation product of aflatoxin B_1.

Use

Aflatoxins are used solely for research purposes. They are naturally occurring contaminants formed by certain fungi on agricultural crops, first discovered in the 1960s (IARC 1976).

Production

Aflatoxins are produced by several fungus species in the genus *Aspergillus*. *A. flavus* and *A. parasiticus* are responsible for most aflatoxin contamination of food crops worldwide. Although these species have similar geographical ranges, *A. parasiticus* is less widely distributed and is rare in Southeast Asia. *A. flavus* is the most widely reported fungus in foodstuffs. *A. australis*, which occurs in the Southern Hemisphere, is the only other species that may be an important source of aflatoxins. Both *A. flavus* and *A. parasiticus* occur in the warm temperate regions of the United States, but are less abundant there than in tropical regions. *A. flavus* is uncommon in cool temperate regions. Both *A. flavus* and *A. parasiticus* produce aflatoxins B_1 and B_2, and *A. parasiticus* also produces aflatoxins G_1 and G_2. The relative proportions and amounts of the various aflatoxins on food crops depend on the *Aspergillus* species present, pest infestation, growing and storage conditions, and other factors. Contamination generally is higher on crops grown in hot, humid tropical climates, but does occur in temperate climates and varies from year to year. Pre-harvest aflatoxin levels increase during droughts, and post-harvest levels increase when crops are not properly dried before storage or are not protected from insect and rodent infestations. Rapid post-harvest drying and storage in an area with a moisture content of less than 10% can eliminate most contamination (IARC 1976, 1993, 2002).

Aflatoxins are not manufactured in commercial quantities but may be produced in small quantities for research purposes. Total annual production was reported to be less than 100 g (IARC 1993, 2002). No U.S. suppliers for aflatoxins were identified in 2009 (ChemSources 2009).

Exposure

The general population is exposed to aflatoxins primarily by eating contaminated food. Aflatoxin-producing fungi commonly grow on corn and other grains, peanuts, tree nuts, and cottonseed meal; however, *A. parasiticus* is rarely found in corn. Meat, eggs, milk, and other edible products from animals that consume aflatoxin-contaminated feed also are sources of potential exposure. Although aflatoxin levels generally are higher during periods of drought, surveys by the U.S. Food and Drug Administration detected aflatoxins in fewer than half of samples collected from feedstuffs even in drought years (Price *et al.* 1993).

Median total aflatoxin concentrations in corn samples collected in the United States between 1978 and 1983 ranged from less than 0.1 to 80 µg/kg (IARC 1993). Data on contamination of foods compiled in 1995 from 90 countries reported a median aflatoxin B_1 concentration of 4 µg/kg (range = 0 to 30 µg/kg) and a median total aflatoxin concentration of 8 µg/kg (range = 0 to 50 µg/kg) (IARC 2002). The estimated daily dietary intake of aflatoxins in the southeastern United States (based on samples collected from 1960 to 1979) was 2.7 ng/kg of body weight, which was substantially less than the daily

intake estimated for periods before 1960 (197 ng/kg for 1910 to 1934 and 108 ng/kg for 1935 to 1959). The time-weighted average daily intake for 1910 to 1979 was 110 ng/kg for the Southeast, but only 0.34 ng/kg for the North and West (Bruce 1990).

Nursing infants may be exposed to aflatoxins in breast milk (Zarba *et al.* 1992). Aflatoxins were detected in 90 of 264 breast-milk samples collected from nursing mothers in Africa, but were not detected in 120 samples collected from nursing mothers in Kiel, Germany. Aflatoxin M_1 was most frequently detected in breast milk, at concentrations varying seasonally from 0.02 to about 1.8 µg/L, but aflatoxin B_1 was found at the highest concentration, 8.2 µg/L (Somogyi and Beck 1993). Biomarkers that may be used to assess aflatoxin exposure include the aflatoxin-DNA adduct in urine and the aflatoxin-albumin adduct in blood serum (Weaver *et al.* 1998).

Occupational exposure to aflatoxins occurs by inhalation of dust generated during the handling and processing of contaminated crops and feeds. Therefore, farmers and other agricultural workers have the greatest risk of occupational exposure. Of 45 animal-feed production plant workers in Denmark, 7 had detectable levels of aflatoxin B_1 in their blood after working for four weeks in the factory or unloading raw materials from ships (Autrup *et al.* 1993). Aflatoxins were detected at concentrations of 0.00002 to 0.0008 µg/m^3 in respirable dust samples collected in workplace and storage areas at rice and corn processing plants in India (Ghosh *et al.* 1997). Dust samples collected from 28 U.S. farms during harvest and unloading, animal feeding, and bin cleaning contained aflatoxins at concentrations ranging from 0.00004 to 4.8 µg/m^3 (Selim *et al.* 1998). The lowest concentrations were detected during harvest and unloading, and the highest during bin cleaning. Both area and personal samplers were used to determine airborne concentrations of aflatoxins B_1, B_2, G_1, and G_2 in dust samples collected from three food-processing plants (for cocoa, coffee, and spices) in Tuscany, Italy; concentrations ranged from below the level of detection (< 0.000002 µg/m^3) to 0.00013 µg/m^3 (Brera *et al.* 2002).

Regulations

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as hazardous constituents of waste.

Food and Drug Administration (FDA)

Ingredients susceptible to contamination with aflatoxins must comply with FDA rules in the manufacturing and processing of food.

Carbohydrase may be safely used in the production of dextrose from starch, provided that aflatoxin is not present.

Action levels for aflatoxins in foods and animal feed range from 0.5 to 300 ppb.

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Alcoholic Beverage Consumption

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Consumption of alcoholic beverages is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Studies indicate that the risk of cancer from consumption of alcoholic beverages is most pronounced among smokers and at the highest levels of consumption. Consumption of alcoholic beverages has been shown to cause cancer of the mouth, pharynx, larynx, and esophagus. Cohort and case-control epidemiological studies in a variety of human populations are consistent in reporting moderate to strong associations between alcohol consumption and cancer at these four sites, and the risk of cancer increases with increasing consumption level. The effect of a given level of alcoholic beverage intake on the absolute risk of cancer at these four tissue sites is influenced by other factors, especially smoking. However, smoking does not explain the observed increased risk of cancer associated with increased alcoholic beverage consumption. Evidence also supports a weaker, but possibly causal, relationship between alcoholic beverage consumption and cancer of the liver and breast (IARC 1988, Longnecker 1994, Longnecker and Enger 1996).

Since alcoholic beverage consumption was reviewed for listing in the *Ninth Report on Carcinogens* in 2000, the International Agency for Research on Cancer has reevaluated the evidence for the carcinogenicity of alcoholic beverage consumption (Baan *et al.* 2007, Secretan *et al.* 2009) and concluded that there was sufficient evidence of carcinogenicity in humans. The 2007 and 2009 reviews concluded that alcoholic beverage consumption caused cancer of the mouth, pharynx, larynx, esophagus, liver, colorectum, and female breast.

Cancer Studies in Experimental Animals

No adequate studies of the carcinogenicity of alcoholic beverages in experimental animal have been reported. The results of studies specifically examining the carcinogenicity of ethanol in experimental animals do not suggest that the ethanol component of alcoholic bev-

erages is solely responsible for the increased risk of cancer associated with human consumption of alcoholic beverages.

Studies on Mechanisms of Carcinogenesis

The mechanism by which consumption of alcoholic beverages causes cancer in humans has not been established. Increased frequencies of chromosomal aberrations, sister chromatid exchange, and aneuploidy were found in the peripheral-blood lymphocytes of alcoholics. Ethanol-free extracts of some alcoholic beverages caused mutations in bacteria and sister chromatid exchange in cultured human cells (IARC 1988).

Properties

Ethanol and water are the main constituents of most alcoholic beverages. Based on the standard measures for most drinks, the amount of ethanol consumed is similar for beer, wine, and spirits (10 to 14 g). Beer, wine, and spirits also contain volatile and nonvolatile flavor compounds that originate from raw materials, fermentation, wooden casks used for maturation, and synthetic substances added to specially flavored beverages. Although the exact composition of many alcoholic beverages is confidential business information, many studies have identified the organic compounds typically present at low levels. Several of the components and contaminants identified in beer, wine, and spirits are known or suspected human carcinogens, including acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate (urethane), asbestos, and arsenic compounds (IARC 1988).

Use

Alcoholic beverages have been made and used by most societies for thousands of years (IARC 1988). Consumption trends, including overall level of alcohol consumption, beverage choice, age and sex differences, and temporal variations, differ among and within societies. In many cultures, alcohol also has been used in medicine and various pharmaceutical preparations, in religious observances, and in feasting and celebrations.

Production

All alcoholic beverages are produced by the fermentation of fruit or other vegetable matter. Most commercial and home production is of fermented beverages that are classified, based on raw materials and production methods used, as beer, wine, or spirits; smaller quantities of other kinds of fermented beverages (e.g., cider, rice wine, palm wine) also are produced. Beer is produced by fermentation of malted barley or other cereals with the addition of hops. Wine is made from fermented grape juice or crushed grapes; fortified wines include additional distilled spirits. Distilled spirits originate from sources of starch or sugar, including cereals, molasses from sugar beets, grapes, potatoes, cherries, plums, and other fruits; after sugar fermentation, the alcohol content is increased by means of liquid distillation. Although ethanol can be chemically synthesized from ethylene, the alcoholic beverage industry does not synthesize alcohol for use in beverages, because of the presence of impurities from the synthetic process (IARC 1988).

In 1990, the United States produced 4.5 million metric tons (10 billion pounds) of wine, 375 million hectoliters (10 billion gallons) of beer, and 18.5 million hectoliters (490 million gallons) of spirits (ARF 1994). Total world production was 29 million metric tons (6.4 billion pounds) of beer, 1 million hectoliters (26.4 million gallons) of wine, and 58 million hectoliters (1.5 billion gallons) of spirits. In 2008, U.S. per-capita consumption was 21.8 gal of beer, 2.5 gal of wine, and 1.4 gal of distilled spirits (USDA 2010). In 2009, U.S. imports and exports of various categories of beer, wine, distilled spirits, and other alcoholic beverages ranged from millions to billions of liters (USITC 2009).

Exposure

Alcohol consumption showed a downward trend in the United States and many European countries from the turn of the twentieth century until the period between the two world wars. U.S. alcohol consumption increased from the 1940s until the early 1980s and then began a steady decrease. By 1993, consumption reached the lowest level since 1964; apparent per-capita consumption expressed in gallons of pure alcohol per year was approximately 1.6 gal in 1940, 2.2 gal in 1964, 2.8 gal in 1980, and 2.2 gal in 1993. Most of the decrease in alcohol consumption can be attributed to decreased consumption of spirits. While overall alcohol consumption was falling, per-capita consumption of wine and beer in the United States was relatively stable from the early 1980s into the 1990s (Williams *et al.* 1995). Per-capita consumption of wine was the same in 1993 as in 1977, while consumption of spirits fell by almost 35% over the same period. Per-capita consumption of beer decreased from 1981 to 1985, fluctuated thereafter, and in 1993 was 1% below 1977 consumption levels (NIAAA 1997). The total number of drinks consumed in the United States in 1999 was about 65.5 billion for beer, 13.7 billion for wine, and 29.3 billion for distilled spirits. Underage drinkers (aged 12 to 20) consumed 19.7% of the total, and adult excessive drinkers (more than 2 drinks per day) consumed 46.3%. The heaviest adult drinkers (highest 2.5%) consumed 27% of the total (Foster *et al.* 2003).

Since 1971, the Substance Abuse and Mental Health Services Administration has conducted an annual survey on the use of alcohol, tobacco, and illicit drugs by the civilian noninstitutionalized population of the United States aged 12 years or older (SAMHSA 2009). This survey, now called the National Survey on Drug Use and Health (formerly the National Household Survey on Drug Abuse) reports prevalence and trends of alcohol consumption at three levels: (1) current use (at least one drink in the past 30 days), (2) binge use (five or more drinks on the same occasion at least once in the past 30 days), and (3) heavy use (five or more drinks on the same occasion on at least 5 different days in the past 30 days). In the 2008 survey, 51.6% of respondents reported alcohol use during the past year; this was significantly lower than the 61.9% reported in 2000 and the peak of 72.9% reported in 1979 (Foster *et al.* 2003, SAMHSA 2009). In 2008, 51.6% of repondents (about 129 million) were current drinkers, 23.3% (about 58.1 million) were binge drinkers, and 6.9% (about 17.3 million) were heavy drinkers. Both binge and heavy drinking were most prevalent young adults (aged 18 to 25). In all age groups except the youngest (aged 12 to 17), men were more likely than women to report drinking alcohol in the past month (SAMHSA 2009).

Regulations

Bureau of Alcohol, Tobacco, Firearms, and Explosives

Alcoholic beverages sold or distributed in the United States, or to members of the Armed Forces outside the United States, must contain a specified health-warning label.

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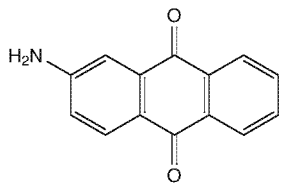
2-Aminoanthraquinone

CAS No. 117-79-3

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

2-Aminoanthraquinone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2-aminoanthraquinone caused tumors in two rodent species and at two different tissue sites. Dietary administration of 2-aminoanthraquinone caused liver cancer (hepatocellular carcinoma) in mice of both sexes and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in male rats. It also caused lymphoma in female mice (NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2-aminoanthraquinone.

Properties

2-Aminoanthraquinone is an aromatic amine that exists at room temperature as red needle-like crystals or a dark-brown granular solid (NCI 1978). It is practically insoluble in water and diethyl ether, slightly soluble in ethanol, and soluble in chloroform, benzene, and acetone (IARC 1982). It decomposes at its melting point (NCI 1978). Physical and chemical properties of 2-aminoanthraquinone are listed in the following table.

Property	Information
Molecular weight	223.2[a]
Density	1.45 g/mL[b]
Melting point	302°C[a]
Log K_{ow}	3.31[a]
Water solubility	0.163 mg/L at 25°C[a]
Vapor pressure	5×10^{-11} mm Hg[c]

Sources: [a]HSDB 2009, [b]Akron 2009, [c]ChemIDplus 2009.

Use

2-Aminoanthraquinone is used as an intermediate in the industrial synthesis of anthraquinone dyes and pharmaceuticals (HSDB 2009). It is the precursor of 22 dyes and 4 pigments, which include the following: C.I. vat blue 4, 6, 12, and 24, vat yellow 1, and pigment blue 22 (NCI 1978). These dyes are used in automotive paints, high-quality paints and enamels, plastics, rubber, and printing inks, and as textile dyes (HSDB 2009).

Production

2-Aminoanthraquinone was first produced commercially in the United States in 1921 (IARC 1982). In 1965, 520,000 kg (1.1 million pounds) was produced in the United States, but production had decreased to 200,000 lb by 1971 (NCI 1978, IARC 1982). In 2009, 2-aminoanthraquinone was produced by five manufacturers worldwide (three in China, one in Europe, and one in India) (SRI 2009) and was available from 21 suppliers, including 10 U.S. suppliers (ChemSources 2009). In 1974, 360,000 lb of 2-aminoanthraquinone was imported into the United States (NCI 1978), but by 2000, imports had decreased to 1 kg (2.2 lb) (USITC 2009). No other data on U.S. imports or exports of 2-aminoanthraquinone were found.

Exposure

The primary route of potential human exposure to 2-aminoanthraquinone is dermal contact (NCI 1978). Consumers may potentially be exposed to 2-aminoanthraquinone through contact with products containing residues of anthraquinone dyes. Data were not available on the levels of 2-aminoanthraquinone impurities in the final dyes, the potential for consumer exposure, or the potential for human uptake. No environmental releases of 2-aminoanthraquinone were reported in the U.S. Environmental Protection Agency's Toxics Release Inventory. If released to the environment, 2-aminoanthraquinone is expected to exist as a particulate in the atmosphere and to be removed by deposition to water and soil. If released to water, it is expected to adsorb to sediment and not volatilize to the atmosphere. In soil, it is expected to be immobile. It is not expected to biodegrade and has a low potential for bioaccumulation (HSDB 2009).

Because 2-aminoanthraquinone is used on a commercial scale solely by the dye industry, the potential for occupational exposure is greatest for workers at dye-manufacturing facilities. No data were available on the number of facilities using 2-aminoanthraquinone or on the numbers of workers potentially exposed.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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USITC. 2009. *USITC Interactive Tariff and Trade DataWeb.* United States International Trade Commission. http://dataweb.usitc.gov/scripts/user_set.asp and search on HTS no. 2922301400. Last accessed: 5/12/09.

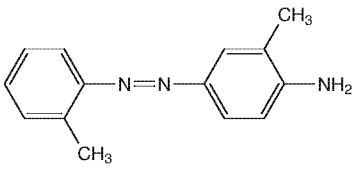
o-Aminoazotoluene

CAS No. 97-56-3

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as C.I. solvent yellow 3 or fast garnet GBC base



Carcinogenicity

o-Aminoazotoluene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

o-Aminoazotoluene caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Dietary administration of *o*-aminoazotoluene caused benign and/or malignant liver tumors in mice of both sexes (hepatocellular adenoma or carcinoma), male rats (adenoma, hepatocellular carcinoma, cholangioma, or other carcinoma), hamsters of both sexes (hepatocellular adenoma or carcinoma), and dogs of unspecified sex (hepatocellular adenoma or carcinoma, adenocarcinoma, or cholangioma). In mice of both sexes, it also caused lung tumors and benign blood-vessel tumors (hemangioendothelioma in the lung). In addition, urinary-bladder cancer was observed in hamsters of both sexes (papillary or transitional-cell carcinoma) and in dogs of unspecified sex (carcinoma); gallbladder tumors in female hamsters (papilloma or carcinoma) and in dogs of unspecified sex (adenocarcinoma); and mammary-gland cancer (adenocarcinoma) in female hamsters (IARC 1975).

Dermal exposure to *o*-aminoazotoluene caused liver tumors in mice of unspecified sex. Administration of *o*-aminoazotoluene by subcutaneous or intramuscular injection caused hepatocellular liver tumors in female mice, rats of unspecified sex, and newborn mice of both sexes (following a single subcutaneous injection). Also observed were lung tumors in adult and newborn mice of both sexes and cancer at the injection site (fibrosarcoma) in female mice. Administration of *o*-aminoazotoluene by intraperitoneal injection caused hepatocellular liver tumors in mice of both sexes. Benign urinary-bladder tumors (papilloma) following intravesicular instillation in mice and intravesicular implantation in rabbits may also have been exposure-related.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *o*-aminoazotoluene.

Properties

o-Aminoazotoluene is an azo dye that exists at room temperature as odorless reddish-brown to golden crystals or an orange powder. It is practically insoluble in water and soluble in alcohol, ether, chloroform, oils, fats, acetone, cellusolve, and toluene. It remains stable under normal temperatures and pressures (IARC 1975, Akron 2009). Physical and chemical properties of *o*-aminoazotoluene are listed in the following table.

Property	Information
Molecular weight	225.3[a]
Density	1.21 g/cm[3][b]
Melting point	101°C to 102°C[a]
Log K_{ow}	3.92[a]
Water solubility	7.64 mg/L at 25°C[a]
Vapor pressure	7.5×10^{-7} mm Hg at 25°C[a]

Sources: [a]HSDB 2009, [b]Akron 2009.

Use

o-Aminoazotoluene is used to color oils, fats, and waxes (IARC 1975). It is also used as a chemical intermediate for the production of the dyes C.I. solvent red 24 and C.I. acid red 115 (HSDB 2009).

Production

Large-scale production of *o*-aminoazotoluene in the United States began in 1914 (IARC 1975). Solvent yellow 3 was manufactured by one U.S. plant in 1979; however, no quantities were reported. In 2009, *o*-aminoazotoluene was produced by one manufacturer in Mexico (SRI 2009) and was available from 19 suppliers worldwide, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of *o*-aminoazotoluene were found.

Exposure

The primary routes of potential human exposure to *o*-aminoazotoluene are dermal contact and inhalation. *o*-Aminoazotoluene is not used directly in foods, drugs, or cosmetics (IARC 1975). The U.S. Environmental Protection Agency's Toxics Release Inventory reported environmental releases of *o*-aminoazotoluene to air in 1988 (250 lb) and 1991 (5 lb) and to surface water in 1990 (5 lb) (TRI 2009). Occupational exposure may occur through inhalation of dust or by dermal contact during production, formulation, or use of *o*-aminoazotoluene (HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,449 workers potentially were exposed to *o*-aminoazotoluene (in the Chemicals and Allied Products and the Transportation Equipment industries); none of these workers were women (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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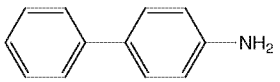
4-Aminobiphenyl

CAS No. 92-67-1

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as para-aminodiphenyl



Carcinogenicity

4-Aminobiphenyl is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Cancer of the urinary bladder was first reported to be associated with occupational exposure to 4-aminobiphenyl in a descriptive epidemiological study (published in the mid 1950s), in which 11% (19 of 171) of workers in a plant manufacturing 4-aminobiphenyl developed urinary-bladder cancer. These workers had been exposed to 4-aminobiphenyl for 1.5 to 19 years between 1935 and 1955. Publication of this study led to an effort to discontinue production and use of 4-aminobiphenyl. Starting in 1955, 541 workers who had been exposed to 4-aminobiphenyl were followed for an additional 14 years; 43 men (7.9%) developed histologically confirmed urinary-bladder cancer. In a survey of workers at a plant producing a variety of chemicals, the risk of mortality from urinary-bladder cancer was elevated tenfold, and all of the men who died of urinary-bladder cancer had worked at the plant during the period when 4-aminobiphenyl was used (1941 through 1952). The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of 4-aminobiphenyl in humans (IARC 1972, 1987).

Since 4-aminobiphenyl was listed in the *First Annual Report on Carcinogens*, most research on its carcinogenicity has focused on exposure from cigarette smoking. Epidemiological studies have reported the incidence of urinary-bladder cancer to be 2 to 10 times as high among cigarette smokers as among nonsmokers. Higher levels of 4-aminobiphenyl adducts (4-aminobiphenyl metabolites bound to DNA or protein) were detected in bladder tumors (DNA adducts) and red blood cells (hemoglobin adducts) from smokers than from nonsmokers (Feng *et al.* 2002). In a case-control study, levels of 4-aminobiphenyl–hemoglobin adducts were higher in smokers with urinary-bladder cancer than in a control group of similarly exposed smokers (Del Santo *et al.* 1991). A Taiwanese study reported that 4-aminobiphenyl–hemoglobin adducts were associated with increased risk of liver cancer (Wang *et al.* 1998).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 4-aminobiphenyl from studies in experimental animals. Oral exposure to 4-aminobiphenyl caused urinary-bladder cancer (carcinoma) in mice, rabbits, and dogs and blood-vessel cancer (angiosarcoma) and liver tumors in mice. 4-Aminobiphenyl administered to rats by subcutaneous injection caused mammary-gland and intestinal tumors (IARC 1987).

Studies on Mechanisms of Carcinogenesis

4-Aminobiphenyl caused genetic damage in several test systems, including mutations in bacteria and in cultured human and other mammalian cells. Other types of genetic damage included mitotic gene conversion in yeast, transformation of cultured mammalian cells, and inhibition of DNA repair in bacteria and cultured mammalian cells. Genetic damage in experimental animals exposed *in vivo* to 4-aminobiphenyl included micronucleus formation, chromosomal aberrations, and sister chromatid exchange (IARC 1987, Shelby *et al.* 1989, GeneTox 1998, HSDB 2009).

The mechanism by which 4-aminobiphenyl causes cancer is thought to require its metabolism to a reactive form. When arylamines, such as 4-aminobiphenyl, are metabolized, they can be either activated via N-hydroxylation (by cytochrome P450 liver enzymes) or detoxified via pathways such as N-acetylation. The *N*-hydroxylamine metabolites can form adducts with blood-serum proteins (such as hemoglobin or albumin), which circulate freely, or they can undergo further transformation to form reactive compounds that can be transported to the bladder and can bind to DNA (Yu *et al.* 2002). 4-Aminobiphenyl–DNA adducts have been found in urinary-bladder epithelial cells from exposed dogs and humans, and 4-aminobiphenyl–protein adducts have been found in serum albumin from exposed rats and in hemoglobin from humans exposed via cigarette smoking (IARC 1987, Feng *et al.* 2002). Moreover, cigarette smokers who were slow acetylators (with inefficient versions of the enzyme *N*-acetyltransferase) had higher levels of 4-aminobiphenyl–hemoglobin adducts than did smokers who were rapid acetylators (Vineis 1994).

Properties

4-Aminobiphenyl is an aromatic amine (arylamine) that exists at room temperature as a colorless crystalline solid with a floral odor. It is slightly soluble in cold water, but readily soluble in hot water. It is soluble in ethanol, ether, acetone, chloroform, and lipids. It oxidizes in air and emits toxic fumes when heated to decomposition (Akron 2009). Physical and chemical properties of 4-aminobiphenyl are listed in the following table.

Property	Information
Molecular weight	169.2
Specific gravity	1.16
Melting point	53.5°C
Boiling point	302°C
Log K_{ow}	2.86 at pH 7.5
Water solubility	0.224 g/L at 25°C
Vapor pressure	5.79×10^{-4} mm Hg at 25°C
Vapor density relative to air	5.8
Dissociation constant (pK_a)	4.35 at 18°C

Source: HSDB 2009.

Use

In the United States, 4-aminobiphenyl now is used only in laboratory research. It formerly was used commercially as a rubber antioxidant, as a dye intermediate, and in the detection of sulfates (HSDB 2009).

Production

Because of its carcinogenic effects, 4-aminobiphenyl has not been produced commercially in the United States since the mid 1950s (Koss *et al.* 1969). It was present in the drug and cosmetic color ad-

ditive D&C yellow no. 1; however, use of this color additive was discontinued in the late 1970s (HSDB 2009). 4-Aminobiphenyl has been reported to be formed by the decomposition of 1,3-diphenyltriazene produced by the reaction of diazoaniline and aniline during manufacture of the dye D&C red no. 33 (Bailey 1985). In 2009, 4-aminobiphenyl (for use in research) was available from 11 U.S. suppliers, including one company that supplied bulk quantities (ChemSources 2009). 4-Aminobiphenyl also has been reported as a contaminant in diphenylamine (HSDB 2009).

Exposure

The potential for exposure to 4-aminobiphenyl is low, because it has no commercial uses. Mainstream cigarette smoke was reported to contain 4-aminobiphenyl at levels of 2.4 to 4.6 ng per cigarette (unfiltered) and 0.2 to 23 ng per cigarette (filtered), and sidestream smoke contained up to 140 ng per cigarette (Patrianakos and Hoffmann 1979, Hoffman *et al.* 1997). 4-Aminobiphenyl may be present in the the color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 at levels established by the FDA (see Regulations). The concentration of 4-aminobiphenyl in D&C red no. 33 was reported to range from 151 to 856 ppb (mean = 567 ppb) for 10 commercial samples of the dye certified by the FDA in 1983; an eleventh sample contained more than 6,500 ppb 4-aminobiphenyl and was reported to be withdrawn by the manufacturer (Bailey 1985). No data were identified on concentrations of 4-aminobiphenyl in foods prepared with any of the dyes in which 4-aminobiphenyl was permitted, but several studies have reported detectable levels of 4-aminobiphenyl adducts in pancreatic DNA (Ricicki *et al.* 2005) and in hemoglobin (Sarkar *et al.* 2006, Peluso *et al.* 2008) in both smokers and nonsmokers.

The U.S. Environmental Protection Agency's Toxics Release Inventory listed only one facility reporting environmental releases of 4-aminobiphenyl, which ranged from 2 to 48 lb per year from 1988 to 2001, except in 1997 and 1998, when no releases were reported. Most of the releases were to underground injection wells; small amounts were released to air in 1988, 1989, and 2000 (TRI 2009).

At greatest risk for occupational exposure are laboratory technicians and scientists who use 4-aminobiphenyl in research.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

The color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 may contain 4-aminobiphenyl at maximum levels that range from 5 to 275 ppb.

The color additive Ext. D&C yellow no. 1 is banned because of contamination with 4-aminobiphenyl.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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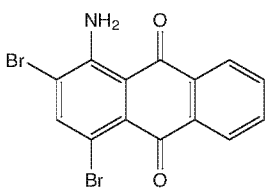
1-Amino-2,4-dibromoanthraquinone

CAS No. 81-49-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as ADBAQ



Carcinogenicity

1-Amino-2,4-dibromoanthraquinone (ADBAQ) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to ADBAQ caused tumors at several different tissue sites in rats and mice. ADBAQ administered in the diet caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in rats and mice of both sexes. In rats of both sexes, it also caused cancer of the large intestine (carcinoma) and urinary bladder (transitional-cell carcinoma) and increased the combined frequency of benign and malignant kidney tumors (renal-tubule adenoma and carcinoma). In mice of both sexes, it also caused cancer of the forestomach (squamous-cell carcinoma) and increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) (NTP 1996).

Cancer Studies in Humans

Two epidemiological cohort studies evaluated the risk of cancer among workers in plants manufacturing anthraquinone dyes; however, it is not known whether workers were exposed specifically to ADBAQ (Gardiner *et al.* 1982, Delzell *et al.* 1989). Some evidence suggests that anthraquinone-dye workers may have an increased risk of cancer. Significant excesses of esophageal and prostate cancer occurred among workers in some areas of an anthraquinone-dyestuffs plant in Scotland, and excesses of lung and central-nervous-system cancer occurred among workers at a New Jersey anthraquinone dye and epichlorohydrin plant (Barbone *et al.* 1992, 1994, Sathiakumar and Delzell 2000). Nevertheless, estimates of risk in all studies were based on small numbers of cancer deaths, and workers may have been exposed to other carcinogens.

Studies on Mechanisms of Carcinogenesis

ADBAQ is rapidly absorbed from the gastrointestinal tract and distributed to most soft tissues. The majority of ADBAQ is metabolized, and both ADBAQ and its metabolites are excreted in the feces and urine. However, the metabolites of ADBAQ have not been identified (NTP 1996). Evaluation of ADBAQ's genetic effects has been hindered by its limited solubility. ADBAQ caused mutations in some strains of bacteria but not in cultured rodent cells, which were tested at lower concentrations (Haworth *et al.* 1983, NTP 1996). In cultured mammalian cells, ADBAQ caused chromosomal aberrations and sister chromatid exchange; however, the results varied among laboratories and among trials at the same laboratory (Loveday *et al.* 1990, NTP 1996). Point mutations in the *ras* proto-oncogene occurred at a higher frequency in forestomach and lung tumors from the two-year carcinogenicity study of ADBAQ-exposed mice than in spontaneous tumors from control mice not exposed to ADBAQ. The predominant types of mutations were A to T transversions and A to G transitions, suggesting that ADBAQ or its metabolites target adenine bases in the *ras* proto-oncogene (Hayashi *et al.* 2001).

The mechanism by which ADBAQ causes cancer is not known. Four other anthraquinones (2-aminoanthraquinone, 1-amino-2-methylanthraquinone, danthron [1,8-dihydroxyanthraquinone], and disperse blue 1 [1,4,5,8-tetraaminoanthraquinone]) are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. There is no evidence to suggest that mechanisms by which ADBAQ causes tumors in experimental animals would not also operate in humans.

Properties

ADBAQ is an anthraquinone-derived vat dye that is a reddish-brown to orange powder at room temperature (NTP 1996). It is insoluble in water, making it a colorfast dye. Physical and chemical properties of ADBAQ are listed in the following table.

Property	Information
Molecular weight	381[a]
Melting point	221°C[a]
Log K_{ow}	5.31[b]
Water solubility	0.000015 g/L at 25°C[b]
Vapor pressure	1.44×10^{-7} mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

ADBAQ and other aminoanthraquinones are key intermediates in the production of almost all anthraquinone dyes (HSDB 2009). Anthraquinones, including ADBAQ, are widely used as starting material for the manufacture of vat dyes, which are a class of water-insoluble dyes that can easily be reduced to a water-soluble and usually colorless form. In this form, they are readily impregnated into fibers and textiles. Oxidation then produces an insoluble colored form that is remarkably fast to washing, light, and chemicals. Vat dyes typically are used with cotton, wool, and cellulose acetate (NTP 1996).

Production

ADBAQ is prepared from 1-aminoanthraquinone by bromination in dilute mineral acids (HSDB 2009). In 2009, ADBAQ was produced by one manufacturer in China and was available from at least five U.S. suppliers (SRI 2009, ChemSources 2009). In 1991, U.S. production of all vat dyes totaled 14 million kilograms (31 million pounds) (NTP 1996).

Exposure

The primary route of potential exposure to ADBAQ is through dermal contact. Because ADBAQ has a very low vapor pressure, inhalation exposure to vapor is unlikely; however, contaminated dust particles could be inhaled. ADBAQ is not known to be formed naturally in the environment, but may be released into the environment during its production or through its use in the production of anthraquinone dyes. ADBAQ was detected in raw wastewater of a dye manufacturing plant in four of eight samples, at concentrations of 92 to 170 ppb. However, it was not detected in the final effluent before its release into a nearby river or in sediments from the river, which suggests that ADBAQ may have been biodegraded or adsorbed to sludge during wastewater treatment (HSDB 2009). No information was found on occupational exposure specifically to ADBAQ or to anthraquinone dyes in general; however, epidemiological studies indicated occupational exposure to anthraquinone dyes in a New Jersey dye and resin manufacturing plant (Sathiakumar and Delzell 2000).

Regulations

No regulations or guidelines relevant to reduction of exposure specifically to ADBAQ were identified.

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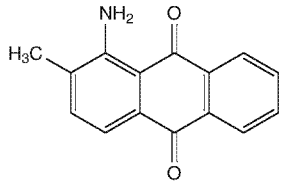
1-Amino-2-methylanthraquinone

CAS No. 82-28-0

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

1-Amino-2-methylanthraquinone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1-amino-2-methylanthraquinone caused tumors in two rodent species and at two different tissue sites. Dietary administration of technical-grade 1-amino-2-methylanthraquinone increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female mice. In rats, it caused liver cancer in both sexes and increased the combined incidence of benign and malignant kidney tumors (tubular-cell adenoma and carcinoma and adenocarcinoma) in males (NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 1-amino-2-methylanthraquinone.

Properties

1-Amino-2-methylanthraquinone is an anthraquinone dye and dye intermediate that exists as an orange solid at room temperature (NCI 1978). It is practically insoluble in water; soluble in acetone, benzene, ethanol, ethylene glycol, monoethyl ether, and linseed oil; and slightly soluble in carbon tetrachloride (IARC 1982, ChemIDplus 2009). Physical and chemical properties of 1-amino-2-methylanthraquinone are listed in the following table.

Property	Information
Molecular weight	237.3[a]
Melting point	206°C[a]
Log K_{ow}	4.07[b]
Water solubility	0.332 mg/L at 25°C[b]
Vapor pressure	3.82×10^{-8} mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

1-Amino-2-methylanthraquinone was used almost exclusively as a dye and as an intermediate in the production of dyes. It was used as a dye for synthetic fibers, furs, and thermoplastic resins. The only dyes derived from 1-amino-2-methylanthraquinone that were produced in the United States were C.I. acid blue 47, last produced in 1973, and C.I. solvent blue 13, last produced in 1974 (IARC 1982, HSDB 2009).

Production

U.S. production of 1-amino-2-methylanthraquinone began in 1948 and ended in 1974 (IARC 1982). In 2009, 1-amino-2-methylanthraquinone was produced by one manufacturer in Europe (SRI 2009) and was available from twelve suppliers, including three U.S. suppliers (ChemSources 2009). U.S. imports of 1-amino-2-methylanthraquinone were last reported in 1972, when 120 kg (265 lb) was imported (IARC 1982).

Exposure

The primary routes of potential human exposure to 1-amino-2-methylanthraquinone are inhalation and dermal contact. The potential for exposure is limited, because 1-amino-2-methylanthraquinone is no longer produced commercially in the United States or reported to be imported. No data were found on environmental releases of 1-amino-2-methylanthraquinone. The potential for occupational exposure was greatest among workers engaged in textile dyeing; however, no data were found on the numbers of workers potentially exposed (HSDB 2009).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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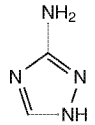
Amitrole

CAS No. 61-82-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Amitrole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Amitrole caused tumors in two rodent species, at two different tissue sites, and by two different routes of exposure. Amitrole caused cancer of the thyroid gland (follicular-cell carcinoma) and liver tumors (hepatocellular tumors) when administered to rats of both sexes in the feed or drinking water and to 7-day-old weanling mice of both sexes by stomach tube for three weeks and in the diet starting at four weeks of age. It also caused liver and thyroid-gland tumors in rats (of unspecified sex) when administered by subcutaneous injection (IARC 1974, Tsuda *et al.* 1976).

Since amitrole was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Dietary administration of amitrole caused cancer of the thyroid gland (follicular-cell carcinoma) in rats of both sexes and marginally increased the incidence of benign pituitary-gland tumors (adenoma) in female rats (IARC 1986, 1987, 2001). Dietary administration of amitrole to female mice nursing pups and then to the weaned offspring caused liver cancer (hepatocellular carcinoma) in the male offspring (IARC 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to amitrole. A small cohort study of Swedish railroad workers who had sprayed herbicides found a statistically significant excess of all cancers among those exposed to both amitrole and chlorophenoxy herbicides, but not among those exposed mainly to amitrole (IARC 1974).

Properties

Amitrole is a triazole compound that is a colorless to white crystalline solid at room temperature (Akron 2009, HSDB 2009). It forms salts with most acids and bases and is a powerful chelating agent (IPCS 1994). It is soluble in water, ethanol, methanol, chloroform, and acetonitrile; sparingly soluble in ethyl acetate; and insoluble in acetone (HSDB 2009). Amitrole is stable under normal temperatures and pressures, but decomposes on exposure to light (Akron 2009). Physical and chemical properties of amitrole are listed in the following table.

Property	Information
Molecular weight	84.1[a]
Specific gravity	1.14 mg/mL at 20°C[a]
Melting point	159°C[a]
Log K_{ow}	–0.97[a]
Water solubility	280 g/L at 25°C[a]
Vapor pressure	4.4×10^{-7} mm Hg at 25°C[a]
Dissociation constant (pK_a)	4.2[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Amitrole was first registered for use as an herbicide in the United States in 1948 but was not commercialized until the 1950s (EPA 1996). In 1958, food-crop use was limited to post-harvest application to cranberries (EPA 1996, IARC 2001). Registrations for use on food crops were cancelled by the U.S. Environmental Protection Agency in 1971, after which amitrole was used primarily as a non-selective terrestrial post-emergent herbicide in outdoor industrial areas, non-agricultural rights of way, and non-agricultural uncultivated areas to treat vines, shade trees, ornamental shrubs and trees, and soil. Amitrole has a wide spectrum of activity against annual and perennial broad-leaf and grass-type weeds. Approved uses on soil were for non-crop land prior to sowing and for inter-row weed control in tree and vine crops, where contact with food plants was avoided (IPCS 1994). Limitations on the use of amitrole included not feeding or grazing animals on land treated with amitrole and not applying it directly to water or wetlands. Amitrole was usually applied by fixed-boom sprayers attached to tractors, trucks, or railroad wagons (EPA 1996, IARC 2001).

Production

Amitrole was first synthesized in 1898 (IARC 2001). At one time, 40 registered pesticide products contained amitrole as an active ingredient; however, no active registered products in the United States now contain amitrole (EPA 2009). Amitrole was not reported to be produced commercially in the United States in surveys conducted in 1978 and 1982 (HSDB 2009). In 2009, amitrole was produced by one manufacturer in Europe and two manufacturers in East Asia (SRI 2009) and was available from 34 suppliers, including 23 U.S. suppliers (ChemSources 2009). Reported U.S. imports of amitrole were 1.2 million pounds in 1978, but had declined to 465,000 lb by 1982 (HSDB 2009). No data on U.S. imports or exports after 1985 were found. A report filed in 1990 under EPA's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of amitrole totaled 10,000 to 500,000 lb (EPA 2004); no inventory update reports were filed for amitrole in 1994, 1998, or 2002.

Exposure

The routes of potential human exposure to amitrole are inhalation, dermal contact, and ingestion (HSDB, 2009). Exposure of the general population could occur through ingestion of contaminated drinking water. Because amitrole is not registered for food-crop uses, there is no known dietary exposure. In 1958 and 1959, amitrole residues were found on cranberries (EPA 1996, HSDB 2009). No amitrole residues were detected in food or water when recommended use practices were followed (IPCS 1994). Exposure could previously have occurred through inhalation near herbicide manufacturing or spraying areas. Large quantities of amitrole previously were used as an herbicide in the United States. In California alone, 82,000 kg (180,000 lb) was used in 1970 and 64,000 kg (141,000 lb) was used in 1972 (IARC 1974). EPA estimated that annual use was 500,000 to 800,000 lb in 1984, declining to between 50,000 and 100,000 lb in 1989 and between 40,000 and 60,000 lb in 1990 (EPA 1996). One death from ingestion of a weed killer containing a mixture of amitrole and ammonium thiocyanate was reported; amitrole was measured in the blood of the victim at 13 mg/L over 12 hours after ingestion (Legras *et al.* 1996).

According to EPA's Toxics Release Inventory, 176 lb of amitrole was released to the environment in 1999, mostly to off-site facilities, and slightly over 100 lb was released in 2007, to off-site facilities. The largest total annual releases were of 265 lb to off-site landfills in 2001 (TRI 2009). When amitrole is released to air, it reacts with photochemically produced hydroxyl radicals, with a half-life of 3 days (EPA

1996, HSDB 2009). It was measured in the air near a manufacturing facility at concentrations as high as 100 μg/m^3 (IPCS 1994). In water and soil, amitrole is not expected to hydrolyze, but it is readily biodegraded by soil microorganisms; it is not likely to bioaccumulate in aquatic organisms. Amitrole is moderately persistent under aerobic conditions, with half-lives of 57 days in water and 22 to 26 days in soil, but it is more persistent under anaerobic conditions, with a half-life of over 1 year in water (EPA 1996, HSDB 2009). Amitrole is highly mobile in alkaline or neutral soils and leaches into groundwater, but it can be bound moderately by cation-exchange reactions in acidic soils, resulting in moderate mobility (EPA 1996, IPCS 1994). Concentrations of amitrole in a river downstream from a production plant ranged from 0.5 to 2 mg/L (IPCS 1994). When amitrole was sprayed on a watershed in Oregon for control of weeds, it was detected in the stream 30 minutes after the aerial spray application at a concentration of 155 μg/L, but not after 6 days (detection limit = 2 μg/L) (Marston *et al.* 1968).

Occupational exposure to amitrole could have occurred during its manufacture, packaging, or application as a herbicide. Particulates containing amitrole could have been released during its production (IPCS 1994). Those most likely to have been exposed were pesticide mixers, loaders, and applicators (EPA 1996). In Sweden, railroad workers exposed during spraying of track areas reported both inhalation exposure and dermal exposure due to wet spray on the hands and face (Axelson *et al.* 1980). According to the National Occupational Exposure Survey (conducted from 1981 to 1983), 693 workers potentially were exposed to amitrole, including 24 women (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of amitrole = U011.

Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 mg/m^3.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.2 mg/m^3.
Listed as a potential occupational carcinogen.

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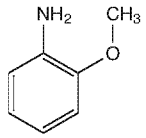
o-Anisidine and Its Hydrochloride

CAS Nos. 90-04-0 and 134-29-2

Reasonably anticipated to be human carcinogens

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

o-Anisidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *o*-anisidine administered as its hydrochloride salt caused tumors in two rodent species and at two different tissue sites. Dietary administration of *o*-anisidine hydrochloride increased the combined incidence of benign and malignant urinary-bladder tumors (transitional-cell papilloma and carcinoma) in rats and mice of both species. In male rats, it also caused kidney cancer (transitional-cell carcinoma of the renal pelvis) and increased the combined incidence of benign and malignant thyroid-gland tumors (follicular-cell adenoma and carcinoma, papillary cystadenoma, and cystadenocarcinoma) (NCI 1978, IARC 1982).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *o*-anisidine or *o*-anisidine hydrochloride.

Properties

o-Anisidine is an aromatic amine that exists at room temperature as a liquid with an amine-like odor and ranging in color from colorless to yellowish, pink, or reddish. It is soluble in water, miscible with etha-

nol, benzene, diethyl ether, and acetone, and soluble in dilute mineral acids. *o*-Anisidine hydrochloride is a salt of *o*-anisidine. It is a gray-black crystalline solid or light gray powder at room temperature and is soluble in water (HSDB 2009). Physical and chemical properties of *o*-anisidine and its hydrochloride salt are listed in the following table.

Property	o-Anisidine	o-Anisidine HCl
Molecular weight	123.2	159.6
Specific gravity	1.10 at 15°C/15°C	NR
Melting point	5°C	225°C
Boiling point	225°C	NR
Log K_{ow}	1.18	NR
Water solubility	14 g/L at 25°C	soluble
Vapor pressure	0.08 mm Hg at 25°C	0.414 mm Hg at 25°C
Vapor density relative to air	4.25	6.77
Dissociation constant (pK_a)	4.53	NR

Source: HSDB 2009. NR = not reported.

Use

o-Anisidine hydrochloride is used as a chemical intermediate in the production of numerous azo and triphenylmethane dyes and pigments (e.g., C.I. direct red 72, disperse orange 29, direct yellow 44, direct red 24, and acid red 4); in the production of pharmaceuticals, including the expectorant guaiacol; as a corrosion inhibitor for steel; and as an antioxidant for polymercaptan resins (IARC 1999, HSDB 2009).

Production

o-Anisidine was produced commercially in the United States from the 1920s until 1957 (IARC 1982). In 2009, six manufacturers of *o*-anisidine were identified worldwide, but none for the hydrochloride salt (SRI 2009). *o*-Anisidine was available from 44 suppliers, including 20 U.S. suppliers, and the hydrochloride salt was available from 8 suppliers, including 5 U.S. suppliers (ChemSources 2009). U.S. imports of *o*-anisidine and its hydrochloride salt are reported in the category "*o*-anisidines, *p*-anisidines, and *p*-phenetidine," and U.S. exports are reported in the category "anisidines, dianisidines, phenetidines and their salts." From 1989 to 2008, imports in the category ranged from a high of over 4.6 million kilograms (10.1 million pounds) in 1996 to zero in 2007 and 2008, and exports ranged from zero to 262,000 kg (577,000 lb) (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *o*-anisidine totaled 500,000 lb to 1 million pounds in 1986, 1990, and 2006; 1 million to 10 million pounds in 1990 and 1998; and 10,000 to 500,000 lb in 2002 (EPA 2004, 2009).

Exposure

The primary routes of potential human exposure to *o*-anisidine and *o*-anisidine hydrochloride are inhalation and dermal contact; exposure may also occur by ingestion (HSDB 2009). Individuals in the population could be exposed to *o*-anisidine in the environment. o-Anisidine occurs in cigarette smoke and as an environmental pollutant in wastewater from oil refineries and chemical plants (IARC 1982, 1999). Mean concentrations of *o*-anisidine in smoke from market, reference, and other cigarettes were reported to range from less than 0.2 to 5.12 ng per cigarette (Stabbert *et al.* (2003). *o*-Anisidine was detected at concentrations ranging from less than 0.05 to 4.2 µg/L (median = 0.22 µg/L) in urine samples from 20 members of the general population in Germany (Weiss and Angerer 2002). Hemoglobin adducts of *o*-anisidine were detected in all blood samples from 224 children in three German cities; however, adduct levels did not differ significantly between children exposed to environmental tobacco smoke and unexposed children (Richter *et al.* 2001).

According to EPA's Toxics Release Inventory, environmental releases of *o*-anisidine between 1988 and 1992 peaked in 1989, when 10,000 lb was released, including almost 5,000 lb to surface water. During this period, most releases were to air; however, 250 lb was released to landfills annually from 1989 through 1992, and 2,000 to 3,600 lb to surface impoundments in 1989, 1991, and 1992. From 1993 to 2007, releases were much lower and remained fairly steady; in 2007, releases totaled 638 lb. Relases of hydrochloride salt have not been reported (TRI 2009). If released to air, *o*-anisidine is expected to remain in the vapor phase and to be degraded by reaction with hydroxyl radicals, with a half-life of 6 hours. If released to surface water, it is expected to bind to sediment or suspended solids with high organic matter content and to volatilize from water with an estimated half-life of 31 days from streams and 350 days from lakes. *o*-Anisidine has little potential to bioaccumulate in aquatic organisms. If released to soil, it will likely bind to humic materials; at low concentrations, it will be subject to rapid biodegradation under aerobic conditions (HSDB 2009).

Occupational exposure to *o*-anisidine and its hydrochloride salt may occur during their production and use as a chemical intermediate, corrosion inhibitor, or antioxidant (IARC 1999). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 705 workers in the Chemicals and Allied Products industry potentially were exposed to *o*-anisidine and 1,108 workers in the same industry potentially were exposed to *o*-anisidine hydrochloride (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: o-Anisidine is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 0.5 mg/m^3 for *o*-anisidine.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m^3 for *o*-anisidine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 mg/m^3 for *o*-anisidine.
Recommended exposure limit (REL) = 0.5 mg/m^3 for *o*-anisidine.
o-Anisidine is listed as a potential occupational carcinogen.

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Aristolochic Acids

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Twelfth Report on Carcinogens* (2011)

Carcinogenicity

Aristolochic acids are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans and supporting data on mechanisms of carcinogenesis. Evidence of carcinogenicity from studies in experimental animals supports the findings in humans.

Cancer Studies in Humans

The evidence for carcinogenicity in humans is based on (1) findings of high rates of urothelial cancer, primarily of the upper urinary tract, among individuals with renal disease who had consumed botanical products containing aristolochic acids and (2) mechanistic studies in humans which demonstrate that aristolochic acids are the carcinogenic agents in these products.

Evidence for the carcinogenicity of aristolochic acids was first identified in studies of Belgian patients with nephropathy (progressive interstitial renal fibrosis) related to the consumption of herbal medicines. The patients had consumed Chinese herbal medicines that were inadvertently contaminated with plant species of the genus *Aristolochia.* Aristolochic acids were considered to be the cause of the nephropathy (now referred to as "aristolochic acid nephropathy," or AAN) because (1) the nephropathy developed immediately after ingestion of the herbs, (2) in most cases, the patients had not been exposed to other agents known to be risk factors for nephropathy, (3) aristolochic acids were identified in the herbal products, and (4) aristolochic acid metabolites bound to DNA (AA-DNA adducts) were found in tissues (usually kidney or urothelial tissue) from some of the patients. Over 100 cases of AAN have been reported in Belgium and over 170 cases in other locations, including the United States, Great Britain, Japan, Taiwan, and China (Arlt *et al.* 2002, NTP 2008).

Two prevalence studies in Belgium (at Cliniques Universitaires St.-Luc and Hospital Erasme) reported high rates of urothelial cancer (40% to 46%), mainly of the upper urinary tract, among female AAN patients who had received kidney transplants (Cosyns *et al.* 1999, Nortier *et al.* 2000, Nortier and Vanherweghem 2002). This rate of urothelial cancer among AAN patients is much higher than the incidence or prevalence of transitional-cell carcinoma of the urinary tract (i.e., urothelial carcinoma) (0.89% to 4%) reported in several studies of Chinese patients with renal disease, either renal-transplant patients or dialysis patients (Ou *et al.* 2000, Wu *et al.* 2004, and Li *et al.* 2008). Neither prevalence study had an unexposed comparison group. Both studies identified aristolochic acids in the botanical products consumed by the patients, and both studies detected AA-DNA adducts in kidney tissue from the patients, demonstrating that the patients had been exposed to aristolochic acids. In the study at Hospital Erasme, the rate of urothelial cancer was significantly higher among AAN patients who had consumed a high dose of the plant *Aristolochia fangchi* than among patients who had consumed a lower dose. Furthermore, AAN patients with and without urothelial cancer did not differ significantly with respect to other risk factors for urothelial cancer, such as smoking or the use of analgesics or nonsteroidal anti-inflammatory drugs. A 15-year follow-up study of AAN patients from Hospital Erasme found a rate of upper-urinary-tract urothelial cancer similar to that previously reported by Nortier and colleagues (Lemy *et al.* 2008). In addition, AAN patients with upper-urinary-tract urothelial cancer had an unusually high incidence of urinary-bladder urothelial cancer.

Additional case reports and clinical investigations of urothelial cancer in AAN patients outside of Belgium support the conclusion that aristolochic acids are carcinogenic (NTP 2008). The clinical studies found significantly increased risks of transitional-cell carcinoma of the urinary bladder and upper urinary tract among Chinese renal-transplant or dialysis patients who had consumed Chinese herbs or drugs containing aristolochic acids, using non-exposed patients as the reference population (Li *et al.* 2005, 2008).

Molecular studies suggest that exposure to aristolochic acids is also a risk factor for Balkan endemic nephropathy (BEN) and upper-urinary-tract urothelial cancer associated with BEN (Grollman *et al.* 2007). BEN is a chronic tubulointerstitial disease of the kidney, endemic to Serbia, Bosnia, Croatia, Bulgaria, and Romania, that has morphology and clinical features similar to those of AAN. It has been suggested that exposure to aristolochic acids results from consumption of wheat contaminated with seeds of *Aristolochia clematitis* (Ivic 1970, Hranjec *et al.* 2005, NTP 2008). AA-DNA adducts were found in kidney tissue from BEN patients and in urothelial and kidney (renal cortical) tissues from BEN patients who had upper-urinary-tract urothelial cancer. Furthermore, A:T to T:A transversion mutations in the *p53* tumor-suppressor gene were found in urothelial tumors from BEN patients (Grollman *et al.* 2007).

The available studies are limited in their ability to formally address confounding by other factors that could increase the risk of cancer, and the case-series studies did not include unexposed controls; however, a causal association between exposure to aristolochic acids and human cancer is evidenced by the strength of the association, consistency across studies, dose-response effects, detection of AA-DNA adducts in exposed patients, timing of the exposure and disease, and specific mutations in the *p53* gene similar to the A:T to T:A transversions seen in rodents and rodent cell cultures exposed to aristolochic acids. The finding of urothelial cancer among patients who consumed a variety of botanical products from different plant species known to contain aristolochic acids provides additional support for the role of aristolochic acids as the cancer-causing agent in the botanical products. In 2000, the International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of herbal remedies containing plant species of the genus *Aristolochia* in humans (IARC 2002). In 2008, IARC concluded that aristolochic acids also were carcinogenic to humans (Grosse *et al.* 2009).

Studies on Mechanisms of Carcinogenicity

Aristolochic acids are absorbed after oral exposure; no data are available on absorption after dermal or inhalation exposure (NTP 2008). Aristolochic acids I and II (AAs I and II) are the most widely studied aristolochic acids. Aristolochic acids are metabolized to aristolactams, which are further metabolized to a cyclic *N*-acylnitrenium ion, a reactive intermediate that forms adducts with purine bases (adenine and guanine) in DNA (dA-AAI, dG-AAI, dA-AAII, and dG-AAII). A number of cytosolic and microsomal enzymes (CYP1A1, CYP1A2, NADPH:CYP reductase, prostaglandin H synthase, DT-diaphorase, xanthine oxidase, cyclooxygenase, and NAD(P)H:quinone oxidoreductase) are capable of bioactivating aristolochic acids to the reactive form (NTP 2008).

DNA adducts have been detected *in vitro* in experimental animals exposed to aristolochic acids and in human tissue from individuals exposed to aristolochic acids, including individuals with AAN, BEN, or urothelial cancer associated with AAN or BEN (Grollman *et al.* 2007, NTP 2008). In animals, adducts have been detected in the forestomach and stomach, urinary tract (kidney and urinary bladder), liver, intestine, spleen, and lung. In humans, adducts have been detected in the urinary tract (kidney, ureter, and urinary bladder), liver, and non-target tissues such as pancreas, breast, and lung (NTP 2008). The predominant adduct, dA-AAI, persists for a lifetime in rats and at least 89 months in humans and appears to be responsible for most of the mutagenic and carcinogenic properties of aristolochic acids (NTP 2008).

Aristolochic acids (purified I or II or mixtures) have been shown to be mutagenic in bacteria, cultured cells, and rodents exposed *in vivo*. AA I has been tested the most extensively. In *in vitro* assays, purified aristolochic acids induced mutations in the bacterium *Salmonella typhimurium* and in cultured mammalian cells, including (1) *hprt* mutations in rat fibroblast-like cells and Chinese hamster ovary cells, (2) forward mutations in mouse lymphoma cells, and (3) mutations in the *p53* DNA-binding domain in two studies with fibroblast cell cultures from human *p53* knock-in (Hupki) mice (mice carrying a humanized *p53* gene sequence) (NTP 2008). Mutations were identified in the *p53* DNA-binding domain in one third (6 of 18) to half (5 of 10) of the established Hupki mouse fibroblast cultures; A:T to T:A transversions were predominant, occurring in at least 80% of the cell lines with mutations (Liu *et al.* 2004). Aristolochic acid mixtures or plant extracts caused mutations in *S. typhimurium* and sex-linked recessive lethal mutations in the fruit fly *Drosophila melanogaster* (NTP 2008). In studies with rodents exposed *in vivo*, exposure to aristolochic acid mixtures or plant extracts caused (1) mutations in subcutaneous granulation tissue from Sprague-Dawley rats (Maier *et al.* 1985), (2) mutations of the *lacZ* transgene in forestomach, kidney, and colon tissue from transgenic Muta mice (Kohara *et al.* 2002), and (3) mutations of the *cII* transgene in liver and kidney tissue from transgenic Big Blue rats (Chen *et al.* 2006, Mei *et al.* 2006). A:T to T:A transversions were the predominant mutation type in the Muta mice and Big Blue rats. Exposure to AA I also caused mutations in granulation tissue from Sprague-Dawley rats (Maier *et al.* 1987).

Aristolochic acids have been shown to bind to adenine in codon 61 in the H-*ras* mouse oncogene and to purines in the human *p53* gene. Mutations identified in tumors of rodents exposed to aristolochic acids include A:T to T:A transversions in codon 61 of the c-Ha-*ras* gene in forestomach tumors (from rats and mice), lung tumors (from rats and mice), and ear-duct tumors (from rats). No mutations were identified in tissues from rats with chronic renal failure that had not been exposed to aristolochic acids (Schmeiser *et al.* 1990, 1991). Similar findings have been reported in humans. A:T to T:A transversion mutations of the *p53* gene were identified in a urothelial tumor from an AAN patient (Lord *et al.* 2004) and at a high frequency (78%) in BEN patients with upper-urinary-tract urothelial cancer. The frequency of A:T to T:A transversions of *p53* mutations in bladder and ureter tumors not caused by aristolochic acid exposure was approximately 5% (Grollman *et al.* 2007). Moreover there was concordance between the location of the *p53* A to T transversions and mutations identified in fibroblast cell cultures from human *p53* knock-in (Hupki) mice treated with AA I (Nedelko *et al.* 2008).

Aristolochic acids also caused other types of genetic damage in other test systems with and without mammalian metabolic activation. Aristolochic acids I and II and mixtures caused DNA damage in the SOS chromotest in the bacterium *Escherichia coli,* and aristolochic acid mixtures caused sex-chromosome loss and somatic recombination in *D. melanogaster*. In mammalian cells exposed *in vitro*, aristolochic acid mixtures caused chromosomal aberrations, sister chromatid exchange, and micronucleus formation in human lymphocytes. AA I also caused chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells. Neither AA I nor AA II induced DNA strand breaks in rat liver cells, but aristolochic acids caused DNA damage in a pig kidney cell line (proximal tubular epithelial cells) and in human hepatocellular carcinoma cells. In mammalian *in vivo* studies, aristolochic acids (composition not specified) did not induce unscheduled DNA synthesis in the pyloric mucosa of male rats. DNA damage was reported in kidney cells isolated from male Sprague-Dawley rats administered a single oral dose of an aristolochic acid mixture. One study reported that intravenous injection of aristolochic acid mixtures increased micronucleus formation in polychromatic erythrocytes in bone marrow from NMRI male and female mice, but another study found no increase in micronucleus formation in peripheral blood reticulocytes from male Muta mice exposed orally to a mixture of AAs I and II (NTP 2008).

Together, these findings strongly suggest that exposure to aristolochic acids causes urothelial cancer in humans through formation of DNA adducts (specifically, through binding of the reactive metabolite with adenine) and the resulting transversion mutations in oncogenes.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of aristolochic acids in experimental animals based on studies showing that aristolochic acids caused tumors in rodents and rabbits at several different tissue sites and by several different routes of exposure. Although the studies in which aristolochic acids were administered orally or by injection typically were small and of short duration, they showed clear evidence of carcinogenicity. In nearly all of the studies, aristolochic acids caused urothelial tumors, as they did in humans.

Oral exposure to aristolochic acids caused predominantly forestomach and urinary-tract tumors, and administration by injection caused mainly urinary-tract tumors and connective-tissue tumors (sarcoma) at the injection site (NTP 2008). In female mice, oral exposure to aristolochic acids caused tumors of the forestomach, stomach, kidney, lung, and uterus and malignant lymphoma (Mengs 1988). In several studies in rats, oral exposure to aristolochic acids caused tumors of the forestomach, kidney (renal-cell and renal-pelvis tumors), urinary bladder, ear duct, thymus, small intestine, and pancreas. Single instances were also reported of tumors of the hematopoietic (blood-producing) system, heart, lung, mammary gland, pituitary gland, and peritoneum (NTP 2008). Male Wistar rats receiving daily subcutaneous injections of aristolochic acids developed urothelial carcinoma of the renal pelvis and malignant fibrohistiocytic sarcoma at the injection site (Debelle *et al.* 2002). A single intraperitoneal injection of aristolochic acids initiated liver carcinogenesis in male F344 rats that had also received treatment to stimulate proliferation of liver

cells (Rossiello *et al.* 1993). Aristolochic acids administered to female New Zealand White rabbits by intraperitoneal injection caused kidney tumors, a urinary-tract tumor, and mesothelioma of the peritoneal cavity (Cosyns *et al.* 2001).

Three studies investigated the carcinogenicity of extracts of *Aristolochia* (one study each for *A. manshuriensis*, *A. clematitis*, and *A. contorta*) when administered to rats orally or by injection. Following oral administration, tumors of the forestomach and kidney were the most prevalent findings (Hwang *et al.* 2006), but one study reported tumors of the mammary gland, thyroid gland, and skin (Qiu *et al.* 2000), and one study reported injection-site polymorphocellular sarcoma (Ivic 1970). In one study, rats of both sexes were exposed to a weight-loss regimen of herbal ingredients that contained aristolochic acids; the males developed forestomach tumors (papilloma and squamous-cell carcinoma) (Cosyns *et al.* 1998).

Properties

Aristolochic acids are a family of nitrophenanthrene carboxylic acids that occur naturally in plants in the family Aristolochiaceae. The aristolochic acid content of plants or botanical preparations varies depending on the plant species, where it was grown, the time of year, and other factors. However, aristolochic acid I (also called aristolochic acid A) and its demethoxylated derivative, aristolochic acid II (also called aristolochic acid B) are the predominant forms. AA I is a crystalline solid that is slightly soluble in water. The molar extinction coefficient (ε) for AA I in ethanol is 6,500 at 390 nm, 12,000 at 318 nm, and 27,000 at 250 nm (O'Neil *et al.* 2006). Other selected physical and chemical properties of AA I are listed in the table below. No information was located on the physical or chemical properties of AA II other than its molecular weight of 311.3 (IARC 2002).

Property	Information for AA I
Molecular weight	341.3
Melting point	281°C to 286°C
Log K_{ow}	3.48

Source: IARC 2002.

Use

Aristolochia plants have been used since ancient times in traditional herbal medicines in many parts of the world, and aristolochic acids have been reported to have antibacterial, antiviral, antifungal, and antitumor effects (Kupchan and Doskotch 1962, Zhang *et al.* 2004). The name *Aristolochia* (meaning the best delivery or birth) is thought to be of ancient Greek origin and reflects centuries of use in obstetrics. Other traditional uses include treatment for snakebite, scorpion stings, fever, infection, diarrhea, and inflammation (Arlt *et al.* 2002, Jiménez-Ferrer *et al.* 2005). In contemporary medicine, *Aristolochia* plant extracts have been used in therapies for arthritis, gout, rheumatism, and festering wounds, but these uses were discontinued in Germany and other countries after the carcinogenic and mutagenic properties of aristolochic acids were first reported in the early 1980s (Arlt *et al.* 2002). Other uses of *Aristolochia* plants include cultivation as ornamental plants. Aristolochic acids also have been used in studies of toxicity and carcinogenicity and in biochemical studies as relatively selective inhibitors of the enzyme phospholipase A2 (NTP 2008).

Occurrence and Production

Aristolochic acids have been detected only in plant species belonging to the family Aristolochiaceae, primarily of the genera *Aristolochia* and *Asarum*. More than 30 *Aristolochia* species are native to the United States, and they are present in most states (USDA 2005). The most widely distributed native species include *A. serpentaria* (Virginia snakeroot), *A. tomentosa* (woolly Dutchman's pipe), *A. macrophylla* (pipevine), and *A. clematitis* (birthwort). In addition, some non-native species are grown as ornamentals or have escaped cultivation and become naturalized. Worldwide, there are an estimated 200 to 350 *Aristolochia* species, and virtually all of them contain aristolochic acids (NTP 2008). *Asarum* species (wild gingers) also are widely distributed in the United States. Plants of the genus *Hexastylis*, a group of rare plants endemic to the southeastern United States, were reported to have "unexpectedly high levels" of aristolochic acids (Schaneberg *et al.* 2002)

A number of studies have reported concentrations of AAs I and II in medicinal plants, including several species used in traditional Chinese medicine. Concentrations ranged from 3 to 12,980 ppm for AA I and from not detected to 6,325 ppm for AA II. In *Asarum* species, concentrations of AAs I and II ranged from trace levels to 3,377 ppm. Other studies detected AA IVa at concentrations of 79 to 3,360 ppm of crude drug, aristolactam I at 6 to 358 ppm, and aristolactam II at 14 to 91 ppm (NTP 2008). Hong *et al.* (1994) identified 11 aristolochic acid derivatives, including aristolactams and other compounds, in extracts from *Aristolochia cinnabarina* roots, and Wu *et al.* (1994) identified 14 aristolochic acid derivatives in extracts from stems and roots of *Aristolochia kankauensis*.

Aristolochic acids are produced commercially as reference standards and as research chemicals (IARC 2002). No data were found on U.S. producers or production volume, but in 2004, aristolochic acids were available from nine U.S. suppliers of aristolochic acid A (AA I), one supplier each of aristolochic acids B and D (AAs II and IV), three suppliers of aristolochic acid C (AA IIIa), and three suppliers of aristolochic acid, sodium salt (ChemSources 2004). No specific data on U.S. production, imports, or sales of botanical products that might contain aristolochic acids were found; however, many U.S. suppliers offer products that could contain aristolochic acids. Gold and Slone (2003) identified 112 botanical products that could contain aristolochic acids and were available for purchase over the Internet.

Exposure

Exposure to aristolochic acids may occur through ingestion as a result of intentional or inadvertent use of herbal or botanical products that contain *Aristolochia* or *Asarum* species. Exposure to aristolochic acids through ingestion of flour from wheat contaminated with *A. clematitis* has been proposed as a cause for BEN. Herbal preparations are available in several forms (e.g., capsules, extracts, teas, or dried herbs). Exposure also could potentially occur through direct contact with the plants, either in their natural habitats or as cultivated ornamentals. Direct contact with the leaves of *Asarum canadense* (Canadian snakeroot or wild ginger) has been reported to cause dermatitis (PFAF 2005).

Schaneberg and Khan (2004) purchased from Internet Web sites 25 herbal products suspected of containing aristolochic acids, of which nine were manufactured in the United States and the rest in China. AAs I and II were detected in six of the products, each of which contained six or more types of plants. The U.S. Food and Drug Administration has reported recalls of products containing aristolochic acids beginning in 2000 and continuing with the report of a recall of two products in 2008 (Tou Tong San [Headache Formula] and Du Huo Ji Sheng Tang [Du Huo Joint Relief]) (FDA 2008). Two herbal remedies prepared from *Aristolochia debilis* or *A. contorta* appeared in the official 2005 Chinese pharmacopeia, and three additional entries for drugs derived from *A. debilis*, *A. fangchi*, and *A. manshuriensis* were cancelled in 2003 and 2004 because the content of aristolochic acid in the drugs was high enough to cause AAN (Zhang *et al.* 2006).

In addition to the intentional uses of aristolochic acid-containing plants, herbal preparations can pose a number of quality-related problems, which can lead to inadvertent exposures. These include contamination with prohibited or restricted substances, substitution of ingredients, contamination with toxic substances, and differences between the labeled and actual product contents (MCA 2002).

The complexity of herbal nomenclature systems used in traditional medicines (particularly traditional Chinese medicines) can lead to confusion and increased risk of inadvertent exposure to aristolochic acids (Flurer *et al.* 2001), which was reported for cases in Hong Kong (Liang *et al.* 2006), Belgium (Vanherweghem 1998), and Singapore (Koh *et al.* 2006). Substitutions arising because of name confusion have also been reported between botanicals used in Japanese herbal medicines and botanicals with similar names used in Chinese herbal medicines (Tanaka *et al.* 2001, EMEA 2005). The most extensive exposure resulting from name confusion occurred in the early 1990s in Belgium, where *A. fangchi* was inadvertently substituted for *Stephania tetrandra* to prepare diet pills. The Chinese name for *S. tetrandra* is "fang ji," which is similar to the name for aristolochic acid–containing *A. fangchi* ("guang fang ji"). An estimated 1,500 to 2,000 individuals (primarily women) were exposed to the *Stephania*-labeled powders that contained aristolochic acids ranging from below the detection limit (< 0.02 mg/g) to 2.9 mg/g (2,900 ppm) (Vanherweghem 1998). The resulting maximum dose of aristolochic acids was estimated at 0.025 mg/kg received over an average of 13 months (Grollman *et al.* 2009).

For botanical products, high concentrations or intake of aristolochic acids have been reported in studies from China (AA I at 700 ppm, with estimated AA intake of 110 mg), Taiwan (AA I at up to 19.97 nmol/g and AA II at up to 3.95 nmol/g), Hong Kong (intake of herb from 100 mg to 800 g), Japan (total AA at up to 15.1 ppm), Australia (AA I at up to 40 ppm and AA II at up to 210 ppm), and Switzerland (AA I at up to 440 ppm) (NTP 2008). Chinese patients who developed chronic renal failure had ingested an estimated 0.7 to 1.5 mg of aristolochic acids per day intermittently for 1 to 10 years (Grollman *et al.* 2009).

No estimates were found of the number of people in the United States who are exposed to aristolochic acids in herbal medicines, but two U.S. cases of renal failure resulting from ingestion of herbal products containing aristolochic acids have been reported (Meyer *et al.* 2000, Consumer Reports 2004, Grollman *et al.* 2007). The use of all complementary and alternative medicines increased in the 1990s and 2000s (Barnes *et al.* 2004, Bent and Ko 2004). The Centers for Disease Control and Prevention reported that 10% of adults in the United States ingested herbal medicines in 1999 (Straus 2002), and the total spent on herbs and other botanical remedies in 2001 was $4.2 billion (Marcus and Grollman 2002).

The possibility also exists for exposure to aristolochic acids in food. It has been suggested that contamination of wheat flour by *Aristolochia* species growing as weeds adjacent to wheat fields might be responsible for BEN (Ivic 1970, Hranjec *et al.* 2005). Indeed, seeds of *A. clematitis* have been found commingled with wheat grain during harvest in regions where BEN is endemic (Grollman and Jelaković 2007). It has been estimated that at least 25,000 individuals are suspected of having BEN and that over 100,000 individuals residing in endemic regions could be at risk (DeBelle *et al.* 2008). As noted above, AA-DNA adducts were found in kidney tissue from BEN patients and in urothelial and kidney (renal cortical) tissues from BEN patients who had upper-urinary-tract urothelial cancer. Because *Aristolochia* species are widely distributed and wheat can be traded internationally, there is the potential for worldwide exposure from this source; however, no data were found to support this hypothesis.

Extracts from *Asarum canadense* and *Aristolochia serpentaria* are permitted for use in the United States as flavoring substances in foods or beverages (FDA 2003); *A. serpentaria* has been reported to be used as a spice and to flavors liqueurs or bitters, such as Angostura or Boonekamp bitters, but no information was found on the concentrations of aristolochic acid in these products.

Although occupational exposure to aristolochic acids has not been documented, herbalists potentially are exposed while gathering plants or while preparing or applying botanical products. Gardeners, landscapers, or nursery workers who handle or transplant *Aristolochia* or *Asarum* plants could potentially be exposed to aristolochic acids. Handling *Aristolochia* or *Asarum* plants could result in dermal exposure, which, as of 2010, has been associated only with dermatitis. To reduce the likelihood of accidental ingestion, workers should wash their hands before eating, drinking, or smoking.

Regulations

Food and Drug Administration (FDA)

Federal Food, Drug, and Cosmetic Act as amended by the Dietary Supplement Health and Education Act

Manufacturers and distributors as of 2007 must record adverse events and report to the FDA serious adverse events reported to them about their products.

Label requirements for dietary supplements have been established.

Manufacturers must establish and meet specifications for identity, purity, strength, and composition and for limits on contamination of dietary supplements under current Good Manufacturing Practices (cGMP) regulations published in 2007.

Warnings and Alerts

Food and Drug Administration (FDA)

Warnings issued in 2000 and 2001 (FDA 2000, 2001a,b) covered botanical products that contain aristolochic acids:

- Practitioners who prescribe botanical remedies urged to discard those products containing aristolochic acids.
- Manufacturers and distributors urged to ensure that botanical products are free of aristolochic acids.
- Consumers urged to immediately discontinue use of botanical products that contain or likely contain aristolochic acids.

An import alert issued in 2000 and revised in 2007 provided for the detention of products labeled as *Aristolochia* or any that could be confused with it unless analytical evidence shows no aristolochic acids.

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Arsenic and Inorganic Arsenic Compounds

CAS No. 7440-38-2 (Arsenic)

No separate CAS No. assigned for inorganic arsenic compounds

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as As

Carcinogenicity

Arsenic and inorganic arsenic compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans.

Cancer Studies in Humans

Epidemiological studies and case reports of humans exposed to arsenic or arsenic compounds for medical treatment, in drinking water, or occupationally have demonstrated that exposure to arsenic and inorganic arsenic compounds increases the risk of cancer. Cancer tissue sites include the skin, lung, digestive tract, liver, urinary bladder, kidney, and lymphatic and hematopoietic systems. Skin cancer has been reported in individuals exposed to arsenic for therapeutic reasons, sometimes in combination with cancer at other tissue sites, such as blood-vessel cancer (angiosarcoma) of the liver, intestinal and urinary-bladder cancer, and meningioma (tumors of the membranes covering the central nervous system). However, only skin cancer has been clearly associated with medical use of arsenic in epidemiological studies (IARC 1973, 1980).

Several studies have reported an association between skin cancer and exposure to arsenic in drinking water. Epidemiological studies conducted in Taiwan, in an area where blackfoot disease (a disorder of the peripheral blood vessels caused by arsenic) is endemic, found that exposure to drinking water containing arsenic at concentrations ranging from 0.35 to 1.14 mg/L increased the risks of urinary-bladder, kidney, skin, lung, liver, and colon cancer. Occupational exposure to inorganic arsenic compounds, especially in mining and copper smelting, consistently has been associated with increased risk of lung cancer (predominantly adenocarcinoma, with a slight excess of small-cell cancer); the risk of lung cancer increased with increasing cumulative exposure to arsenic. Exposure of smelter workers to arsenic also has been associated with increased risks of cancer of the kidney, digestive tract, and lymphatic and hematopoietic systems. Epidemiological studies and case reports of workers in other industries exposed to arsenic, such as glass workers, hat makers, and pesticide workers, also have reported excesses of cancer (mainly lung and skin cancer) (IARC 1973, 1980).

Since arsenic was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, numerous epidemiological studies have evaluated the carcinogenicity of arsenic in drinking water. Several studies have reported exposure-response relationships for several types of cancer, including urinary-bladder, kidney, lung, and skin cancer (Cantor 1997, Ferreccio *et al.* 2000). A few studies have suggested that exposure to arsenic in drinking water is associated with cancer at additional tissue sites, including prostate cancer in men and nasal cancer in both sexes (Cantor 1997). Some evidence suggests that arsenic exposure is more strongly associated with transitional-cell carcinoma of the urinary bladder than with other types of urinary-bladder cancer (Guo *et al.* 1997, Chiou *et al.* 2001). Most studies found associations with cancer of the lung, urinary bladder, or prostate at lower arsenic concentrations than those reported in the Taiwanese study cited above; however, the evidence for carcinogenic effects at very low concentrations of arsenic is inconclusive (Kurttio *et al.* 1999, Lewis *et al.* 1999, Ferreccio *et al.* 2000, Chiou *et al.* 2001, Steinmaus *et al.* 2003, Bates *et al.* 2004). In some studies of urinary-bladder cancer, an association with arsenic exposure was observed only when the analysis was limited to smokers and to arsenic exposures that had occurred at least 40 years previously (Steinmaus *et al.* 2003, Bates *et al.* 2004).

Cancer Studies in Experimental Animals

Metallic arsenic, arsenic trioxide, sodium arsenite, sodium arsenate, potassium arsenite, lead arsenate, calcium arsenate, and pesticide mixtures containing arsenic have been tested for carcinogenicity in experimental animals (IARC 1980, 1987). Mice and rats were exposed to various arsenic compounds by oral administration and subcutaneous injection. Mice were also exposed by dermal application, inhalation, and intravenous injection, and rats by intratracheal instillation and femoral intramedullary injection. In other studies, dogs were exposed orally, hamsters by intratracheal instillation, and rabbits by intramedullary injection. In rats, oral exposure to arsenic trioxide caused stomach cancer (adenocarcinoma), and intratracheal instillation of a pesticide mixture containing calcium arsenate compounds caused a high incidence of lung cancer (adenocarcinoma). Benign and malignant lung tumors (adenoma and carcinoma) were also observed at low incidences in hamsters following intratracheal instillation of arsenic trioxide, and benign lung tumors (adenoma) occurred in neonatal mice subcutaneously injected with arsenic trioxide following prenatal exposure via a single subcutaneous injection during gestation. Lymphocytic leukemia and lymphoma were observed in mice given weekly intravenous injections of an aqueous solution of sodium arsenate for 20 weeks and in female mice and their offspring following subcutaneous injections of sodium arsenate throughout pregnancy. In most of the other studies in experimental animals, no tumors were observed, or the results were inconclusive.

Properties

Arsenic is a naturally occurring semimetallic element with an atomic weight of 74.9. Pure arsenic (which rarely is found in nature) exists in three allotropic forms: yellow (alpha), black (beta), and gray (gamma) (HSDB 2009). Many inorganic arsenic compounds are found in the environment, frequently occurring as the sulfide form in complex minerals containing copper, lead, iron, nickel, cobalt, and other metals. Arsenic compounds occur in trivalent and pentavalent forms; common trivalent forms are arsenic trioxide and sodium arsenite, and common pentavalent forms are arsenic pentoxide and the various arsenates. Arsenic and arsenic compounds occur in crystalline, powder, amorphous, or vitreous forms. Elemental arsenic has a specific gravity of 5.73, sublimes at 613°C, and has a very low vapor pressure of 1 mm Hg at 373°C. Many of the inorganic arsenic compounds occur as white, odorless solids with specific gravities ranging from about 1.9 to over 5. Arsenic trioxide, the most common arsenic compound in commerce, melts at 312°C and boils at 465°C (ATSDR 2007). In water, elemental arsenic is insoluble, calcium arsenate and arsenites are sparingly soluble, and arsenic trioxide, arsenic pentoxide, and other arsenicals are soluble. Arsenic pentoxide, potassium arsenite, and the sodium salts are soluble in ethanol. Arsenic, arsenic pentoxide, arsenic trioxide, the calcium arsenites, lead arsenate, and potassium arsenate are soluble in various acids. When heated to decomposition, arsenic compounds emit toxic arsenic fumes (HSDB 2009).

Use

Inorganic arsenic compounds were widely used as pesticides from the mid 1800s to the mid 1900s and were used in medicine until the 1970s, primarily for treatment of leukemia, psoriasis, and asthma. The use

of arsenic for treatment of acute promyelocytic leukemia resumed in the 1990s. By the mid 1970s, arsenic use was shifting from pesticides to wood preservatives, and by 1980, wood preservatives were the primary use. Total agricultural-chemical use (in pesticides and fertilizers) declined to about 15% to 20% of total arsenic consumption by the early 1990s and has remained at about 4% since 1995 (Edelstein 1994, Reese 1998, ATSDR 2007, Brooks 2009).

Since the mid 1990s, arsenic trioxide used in wood preservation has accounted for 86% to 90% of total U.S. arsenic consumption. Wood treated with chromated copper arsenate (CCA), known as "pressure-treated wood," has been used widely to protect utility poles, building lumber, and foundations from decay and insect attack. However, a voluntary phase-out of CCA for certain residential uses (e.g., in wood for decks, play structures, fencing, and boardwalks) that went into effect December 31, 2003, has reduced this use of arsenic. CCA continues to be used in wood products for industrial use. Other uses of arsenic in the 1990s included use in glass (3% to 4%) and nonferrous alloys (1% to 4%) (ATSDR 2007, Brooks 2009).

By the 1990s, there was renewed interest in the use of arsenic for treatment of acute promyelocytic leukemia (ATSDR 2007). Arsenic trioxide is approved by the U.S. Food and Drug Administration for treating this type of leukemia when other chemotherapy treatments have failed (MedlinePlus 2009). Arsenic is also used in the production of lead alloys used in lead-acid batteries. It may be added to alloys used for bearings, type metals, lead ammunition, and automotive body solder, and it may be added to brass to improve corrosion resistance. High-purity arsenic is used in a variety of semiconductor applications, including solar cells, light-emitting diodes, lasers, and integrated circuits (ATSDR 2007).

Production

Before 1985, U.S. arsenic production varied widely, peaking at 24,800 metric tons (54.7 million pounds) in 1944. Although the United States is the world's leading consumer of arsenic, arsenic has not been produced domestically since 1985, when production of 2,200 metric tons (4.9 million pounds) was reported (Brooks 2009, USGS 2009). U.S. apparent consumption of arsenic was estimated at 7,340 metric tons (16.2 million pounds) in 2006, declining steadily to 3,600 metric tons (7.9 million pounds) in 2009 (USGS 2010). All arsenic metal and compounds consumed in the United States now are imported. U.S. imports of arsenic and arsenic compounds averaged about 8,300 metric tons (18.3 million pounds) from 1935 to 1959, 11,200 metric tons (24.7 million pounds) from 1960 to 1985, and 19,000 metric tons (42 million pounds) from 1986 to 2009 (USGS 2009, 2010). Since 2004, imports have ranged from a high of 10,500 metric tons (23.1 million pounds) in 2006 to a low of 5,190 metric tons (11.4 million pounds) in 2008, and were 6,575 metric tons (14.5 million pounds) in 2009, with arsenic trioxide accounting for 94% and arsenic metal accounting for 6% of imports (USGS 2010). U.S. exports peaked at 4,230 metric tons (9.3 million pounds) in 1941 and reached a low of 36 metric tons (79,000 lb) in 1996. Exports have increased dramatically since 2004. Exports classified as arsenic metal may include arsenic-containing e-waste, such as computers and other electronics destined for reclamation and recycling in other countries. Since U.S. arsenic production ended in 1985, exports have been highest in 2005, at 3,270 metric tons (7.2 million pounds). In 2009, exports totaled 2,980 metric tons (6.6 million pounds) (Brooks 2009, USGS 2009, 2010).

Exposure

The general population is exposed to arsenic and arsenic compounds primarily through consumption of foods. The estimated daily dietary intake of inorganic arsenic ranges from about 1 to 20 μg; however, the average daily dietary intake of arsenic in all forms is about 40 μg. The highest levels of arsenic (in all forms) are detected in seafood, rice, rice cereal, mushrooms, and poultry. Inorganic arsenic was reported in the tissue of livestock that had been administered arsenic drugs or feed additives (ATSDR 2007), and U.S. Department of Agriculture researchers reported that consumption of meat from chickens fed an organic arsenic compound (4-hydroxy-3-nitrophenylarsonic acid) could result in ingestion of 21.1 to 30.6 μg of inorganic arsenic per day for people in the 99th percentile of consumption level (Lasky *et al.* 2004). This organic arsenic compound, which is used as an antimicrobial in animal and poultry feeds, is found mostly unchanged in poultry litter; however, under anaerobic conditions, *Clostridium* bacteria can transform it to release arsenate (Stolz *et al.* 2007). The release of inorganic arsenic from large quantities of poultry litter could have a detrimental effect on soil and water quality (Jackson *et al.* 2003). Arsenic used as pigments in paints can be ingested through contamination of hands, fingernails, food, cups, or cigarettes or through the practice of holding paint brushes in the mouth (HSDB 2009).

Potential exposure to arsenic also occurs through the consumption of drinking water contaminated with arsenical pesticides, natural mineral deposits, or arsenical chemicals that were disposed of improperly (ATSDR 2007). Natural soil concentrations of arsenic (in all forms) typically range from 0.1 to 40 mg/kg, averaging 5 to 6 mg/kg. Through natural processes, arsenic in soil can be released to groundwater or surface water. In the United States, mean arsenic concentrations generally are higher in groundwater systems (wells) than in surface-water systems. Arsenic concentrations in groundwater and surface water are lowest in the mid-Atlantic and southeastern regions, intermediate in New England, the Midwest, and the south-central and north-central regions, and highest in the West (EPA 2000). U.S. drinking water contains arsenic at an average concentration of 2 μg/L; however, 12% of groundwater systems in the West and 12% of surface-water systems in the north-central region contain arsenic at levels exceeding 20 μg/L (ATSDR 2007). In addition, several states have groundwater systems with maximum levels of arsenic exceeding 50 μg/L, including California (99 μg/L), Nevada (150 μg/L), and Texas (86 μg/L) (EPA 2000). Reported arsenic concentrations in groundwater in Fairbanks, Alaska, ranged up to 1,670 μg/L (USGS 2001).

The general population may also be exposed to arsenic compounds emitted to the air by pesticide manufacturing facilities, smelters, cotton gins, glass manufacturing operations, cigarette smoking, burning of fossil fuels, and other sources (ATSDR 2007). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental relseases of arsenic between 1988 and 2007 ranged from 77,000 lb to over 77 million pounds, while releases of arsenic compounds ranged from 3.4 million to 568 million pounds. Releases showed no clear trends over this period. In 2007, 51 facilities released arsenic, and 245 facilities released arsenic compounds (TRI 2009).

Inhalation and dermal contact are the primary routes of occupational exposure to arsenic. Because arsenic is no longer produced in the United States and many uses of arsenical pesticides have been banned, the number of workers exposed to arsenic likely has decreased since the early 1980s. Nevertheless, occupational exposure to arsenic (including forms other than inorganic compounds) is likely in several industries, including nonferrous smelting, wood preservation, glass manufacturing, electronics, and production and use of agricultural chemicals (ATSDR 2007). No recent occupational exposure surveys were found; however, the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that over 57,000 workers, including over 11,000 women, potentially were exposed to arsenic, arsenic pentoxide, arsenic trioxide, arsenic acid, arsenic oxide, arsenic sulfide, or arsenic trichloride (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Fireworks devices shall not contain arsenic sulfide, arsenates, or arsenites.

Department of Transportation (DOT)

Inorganic arsenic compounds are considered hazardous materials, and orthoarsenic acid is considered a marine pollutant; special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Arsenic compounds are listed as mobile source air toxics for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Arsenic compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb for arsenous trichloride; = 1,000 lb for arsine.

Urban Air Toxics Strategy: Arsenic compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Limits have been established for arsenic in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Liquid hazardous wastes containing arsenic and/or compounds at levels ≥ 500 mg/L (as As) are prohibited from underground injection.

Effluent Guidelines: Arsenic and arsenic compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.018 µg/L for arsenic; based on fish or shellfish consumption only = 0.14 µg/L for arsenic.

Numerous inorganic arsenic compounds are designated hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for arsenic, arsenic acid, arsenic disulfide, arsenic pentoxide, arsenic trioxide, arsenic trisulfide, arsenic oxide, arsenic trichloride, sodium arsenate, lead arsenate, calcium arsenate, potassium arsenate, sodium arsenite, potassium arsenite, calcium arsenite.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Arsenic and arsenic compounds are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 1 lb for arsenic pentoxide, arsenic disulfide, arsenic trisulfide, arsenic trioxide, arsenous oxide, sodium arsenate, calcium arsenate, arsenous trichloride, sodium arsenite, potassium arsenite, arsenic; = 100 lb for arsine.

Threshold planning quantity (TPQ) = 100 lb for arsine; = 500 lb for arsenous trichloride; = 100 lb/10,000 lb for arsenic pentoxide, arsenic trioxide, arsenous oxide (solids in powder form with particle size < 100 µm or in solution or molten form/all other forms); = 500 lb/10,000 lb for calcium arsenate, sodium arsenite, potassium arsenite; = 1,000 lb/10,000 lb for sodium arsenate.

Federal Insecticide, Fungicide, and Rodenticide Act

The tolerance for residues of arsanilic acid (a plant regulator) on grapefruit = 2 ppm (0.7 ppm total arsenic).

The label of each pesticide must state whether it contains arsenic in any form and the percentage of total and water-soluble arsenic.

Wood intended to be used in residential settings cannot be treated with chromated copper arsenate (CCA).

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of arsenic or its compounds = P010, P011, P012, F032, F034, F035, K031, K060, K084, K101, K102, K161, K171, K172, K176.

Arsenic and arsenic compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.01 mg/L for arsenic.

Food and Drug Administration (FDA)

Maximum permissible level of arsenic in bottled water = 0.01 mg/L.

Specified color additives may be used in food, drugs, and cosmetics subject to limitations on arsenic levels as prescribed in 21 CFR 73 and 74.

Maximum arsenic levels in various specified food additives range from 0.1 to 3 ppm.

All drug products containing potassium arsenite are withdrawn from the market.

Labels must be put on drugs containing arsenic stating that prolonged use could cause serious injury and to keep out of the reach of children.

Tolerances for residues of arsenic in swine, poultry meat and by-products, and chicken eggs range from 0.5 to 2 ppm.

Maximum levels allowed in food additives permitted in feed and drinking water for animals range from 3 to 75 ppm.

Arsenic trioxide is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.010 mg/m^3.

Comprehensive standards for occupational exposure to arsenic have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 mg/m^3 for inorganic arsenic compounds; = 0.005 ppm for arsine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 5 mg/m^3 for inorganic compounds (as As).

Ceiling recommended exposure limit = 0.002 mg/m^3 (15 min) for inorganic compounds (as As).

Inorganic arsenic compounds are listed as potential occupational carcinogens.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Asbestos

CAS No. 1332-21-4

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Asbestos and all commercial forms of asbestos are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Studies in humans have shown that exposure to asbestos causes respiratory-tract cancer, mesothelioma of the lung and abdominal cavity (pleural and peritoneal mesothelioma), and cancer at other tissue sites. Case reports and epidemiological studies have found that occupational exposure to chrysotile, amosite, anthophyllite, mixtures containing crocidolite, and various complex mixtures of asbestos increases the risk of lung cancer (the various forms of asbestos are identified and described below, under Properties). The risk of lung cancer was increased up to sixfold in vermiculite miners exposed to tremolite and actinolite. Mesothelioma and digestive-tract cancer were observed in workers occupationally exposed to crocidolite, amosite, and chrysotile; however, the results for digestive-tract cancer were inconsistent among studies. An excess of laryngeal cancer was reported in studies of shipyard workers, chrysotile miners, insulation workers, and other workers exposed to asbestos. People living near asbestos factories or mines or living with asbestos workers also developed mesothelioma. However, no clear association was found between cancer risk and exposure to asbestos in drinking water. Co-exposure to asbestos and tobacco smoking increased the risk of lung cancer in a synergistic manner (i.e., the effects of co-exposure on risk were multiplicative, rather than additive). The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of asbestos in humans (IARC 1977, 1987).

Since asbestos was listed in the *First Annual Report on Carcinogens,* the evidence for the carcinogenicity of asbestos has been reevaluated by the Institute of Medicine (IOM) of the National Academy of Sciences in 2006 (NAS 2006) and by IARC in 2009 (Straif *et al.* 2009). IARC concluded that exposure to all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) was associated with an increased risk of lung cancer and mesothelioma. In addition, it concluded that there was sufficient evidence from epidemiological studies that asbestos also caused cancer of the larynx and ovary, as well as limited evidence that it caused cancer of the colorectum, pharynx, and stomach. In general, these conclusions were consistent with the IOM evaluation, which found sufficient evidence that exposure to asbestos caused cancer of the larynx and suggestive evidence that it caused cancer of the pharynx, stomach, and colorectum (NAS 2006). The IOM did not review studies on lung cancer and mesothelioma.

Cancer Studies in Experimental Animals

All commercial forms of asbestos have been shown to cause cancer in several species of experimental animals by various routes of exposure (IARC 1977, 1987). Inhalation exposure to chrysotile, crocidolite, amosite, anthophyllite, or tremolite caused mesothelioma and lung cancer (carcinoma) in rats. Intrapleural injection of various types of asbestos caused mesothelioma in rats and hamsters, and intraperitoneal injection of chrysotile, crocidolite, or amosite caused peritoneal tumors, including mesothelioma, in mice and rats. The incidence of abdominal tumors was increased by intraperitoneal injection of crocidolite in hamsters and actinolite or tremolite in rats. When filter material containing chrysotile was added to the diet of rats, the overall incidence of malignant tumors (including kidney, lung, and liver tumors) was increased. Oral administration of amosite, tremolite, or crocidolite did not cause tumors in rats, nor did oral administration of amosite or chrysotile in hamsters (NTP 1985, IARC 1987). Dietary administration of chrysotile asbestos fibers of short or intermediate lengths did not cause tumors in female rats, but dietary exposure to the intermediate-length fibers resulted in a low incidence of benign adenomatous polyps of the large intestine in male rats (NTP 1985).

Asbestos and the polycyclic aromatic hydrocarbon benzo[*a*]pyrene administered alone by intratracheal injection did not cause tumors in rats, but when co-administered caused lung tumors and mesothelioma (IARC 1977). Synergistic effects on tumor induction also were observed following co-administration of asbestos and benzo[*a*]pyrene or asbestos and *N*-nitrosodiethylamine to hamsters (IARC 1987).

IARC (1977, 1987) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of asbestos, including the following forms: actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite. Since asbestos was reviewed for listing in the *First Annual Report on Carcinogens* and by IARC, intrabronchial instillation of chrysotile has been shown to cause pulmonary and pleural mesothelioma in rats (Fasske 1988).

Properties

Asbestos is the generic name for a group of six naturally occurring fibrous silicate minerals, including the fibrous serpentine mineral chrysotile and the five fibrous amphibole minerals actinolite, amosite, anthophyllite, crocidolite, and tremolite. Asbestos minerals possess a number of properties useful in commercial applications, including heat stability, thermal and electrical insulation, wear and friction characteristics, tensile strength, the ability to be woven, and resistance to chemical and biological degradation. The forms are ranked from greatest to least tensile strength as follows: crocidolite, chrysotile, amosite, anthophyllite, tremolite, and actinolite. Their ranking from greatest to least acid resistance is tremolite, anthophyllite, crocidolite, actinolite, amosite, and chrysotile. The forms that have been used commercially are chrysotile, anthophyllite, amosite, and crocidolite (IARC 1977, ATSDR 2001, HSDB 2009).

Chrysotile, the most abundant form of asbestos in industrial applications, occurs naturally in fiber bundle lengths ranging from several millimeters to over 10 cm (Virta 2002a). Chrysotile has an idealized chemical composition of $Mg_3Si_2O_5(OH)_4$ and occurs as a curled sheet silicate, which wraps around itself in a spiral, forming a hollow tubular fiber. The hydroxyl group may, rarely, be replaced by oxygen, fluorine, or chlorine. In addition, small amounts of iron, aluminum, nickel, calcium, chromium, manganese, sodium, or potassium may be present as impurities. Natural chrysotiles occur with a range of phys-

ical properties. Chrysotiles may be white, gray, green, or yellowish, with a silky luster. Although chrysotile fibers are more flexible than the amphiboles, fibers from different geological locations may differ in flexibility. Chrysotile fibers have a net positive surface charge and form a stable suspension in water. The fibers degrade in dilute acids (IARC 1973, 1977, IPCS 1986).

The amphibole forms of asbestos consist of chain structures, with nine structural sites that accommodate cations. Amphibole crystals consist of two chains based on Si_4O_{11} units, linked by a band of cations. The principal cations are magnesium, iron, calcium, and sodium, and their ratios determine the mineral species. The chemical composition and physical properties vary over a wide range, and the chemical composition of a field sample seldom matches the idealized formula. Amphibole fibers do not divide into fibrils as small in diameter or as symmetrical as chrysotile fibers, and they do not have a hollow central core. They have a negative surface charge in water (IPCS 1986, HSDB 2009).

Amosite is ash gray, greenish, or brown and is somewhat resistant to acids. It tends to occur with more iron than magnesium, at a ratio of approximately 5.5 to 1.5. The fibers are long, straight, coarse, and somewhat flexible (less so than chrysotile or crocidolite) (IARC 1973, 1977, IPCS 1986).

Anthophyllite is grayish white, brown-gray, or green and is very resistant to acids. It is relatively rare and occasionally occurs as a contaminant in talc deposits. The fibers are short and very brittle (IARC 1973, 1977, IPCS 1986).

Crocidolite is lavender or blue and has good resistance to acids, but less heat resistance than other asbestos fibers. Its fibers typically are shorter and thinner than those of other amphiboles, but not as thin as chrysotile fibers. The fibers have fair to good flexibility and fair spinnability. Crocidolite usually contains organic impurities, including low levels of polycyclic aromatic hydrocarbons (IARC 1973, 1977, IPCS 1986).

Tremolite is a calcium-magnesium amphibole, and actinolite is an iron-substituted derivative of tremolite. Both occur in asbestos and non-asbestos forms. Tremolite is a common contaminant in chrysotile and talc deposits, and actinolite is a common contaminant in amosite deposits. Tremolite is white to gray, and actinolite is pale to dark green. Both are brittle; tremolite is resistant to acids, but actinolite is not (IARC 1977, IPCS 1986).

Use

Although asbestos use dates back at least 2,000 years, modern industrial use began around 1880. Use of asbestos peaked in the late 1960s and early 1970s, when more than 3,000 industrial applications or products were listed. Asbestos has been used in roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials, coatings, plastics, textiles, paper, and other products (ATSDR 2001, HSDB 2009). The U.S. Consumer Product Safety Commission banned use of asbestos in general-use garments, but asbestos may be used in fire-fighting garments if they are constructed to prevent release of asbestos fibers (HSDB 2009). Domestically used asbestos fibers are classified into seven quality categories or grades. Grades 1, 2, and 3 include the longer, maximum-strength fibers and generally are used in the production of textiles, electrical insulation, and pharmaceutical and beverage filters. Grades 4, 5, and 6 are medium-length fibers used in the production of asbestos-cement pipes and sheets, clutch facings, brake linings, asbestos paper, packaging, gaskets, and pipe coverings. Grade 7 includes short fibers generally used as reinforcers in plastics, floor tiles, coatings and compounds, some papers, and roofing felts (OSHA 1986).

The four commercially important forms of asbestos have been chrysotile, amosite, anthophyllite, and crocidolite (IARC 1973); however, commercial use of anthophyllite was discontinued by the 1980s (IPCS 1986, HSDB 2009). Chrysotile, amosite, and particularly crocidolite all have extremely high tensile strengths and are used extensively as reinforcers in cements, resins, and plastics. Although chrysotile is most adaptable to industrial use, crocidolite and amosite are particularly useful in combination with chrysotile for adding specific properties, such as rigidity (OSHA 1986). By the 1990s, chrysotile accounted for more than 99% of U.S. asbestos consumption (ATSDR 2001). By 2008, chrysotile was the only type of asbestos used in the United States (Virta 2008); 64% of chrysotile used was categorized as grade 7 asbestos (with fiber lengths less than 3 mm), followed by grades 4, 5, and 3 (Virta 2002a, 2009).

In 1973, when U.S. consumption of asbestos was at its peak, the major markets included asbestos cement pipe (24%), flooring (22%), roofing (9%), friction products, such as automobile brakes and clutches (8%), and packing and gaskets (3%) (Virta 2002a). In 2009, roofing products accounted for about 65% of U.S. consumption; the remaining 35% was attributed to "other uses" (USGS 2010).

Production

U.S. demand for asbestos increased dramatically from 1900 to the early 1970s. By 1950, the United States was the world's largest user of asbestos. However, asbestos demand declined rapidly after 1973 as health and liability issues became apparent (Virta 2002a). Before the 1980s, asbestos was produced in California, Arizona, North Carolina, and Vermont; however, most of these facilities suspended mining operations in the 1970s, and the last U.S. asbestos mine closed in 2002 (ATSDR 2001, Virta 2002b). U.S. production of asbestos decreased from a high of 136,000 metric tons (300 million pounds) in 1973 to 2,720 metric tons (6 million pounds) in 2002 (USGS 2009). U.S. asbestos consumption declined from a maximum of 803,000 metric tons (1.8 billion pounds) in 1973 to 715 metric tons (1.6 million pounds) in 2009 (USGS 2009, 2010). In 2010, two U.S. suppliers of asbestos were identified (ChemSources 2009). Most of the asbestos used in the United States is imported from Canada (Virta 2008). U.S. imports of asbestos peaked in 1973, at 718,000 metric tons (1.6 billion pounds) and totaled 715 metric tons (1.6 million pounds) in 2009 (USGS 2009, 2010). U.S. asbestos exports peaked in 1981 at 64,400 metric tons (142 million pounds), declining to 55 metric tons (121,000 pounds) in 2009.

Exposure

The primary routes of potential human exposure to asbestos are inhalation and ingestion. Dermal absorption of asbestos is minimal, but dermal contact may lead to secondary ingestion or inhalation of dust. Asbestos fibers vary with respect to size (length and diameter) and chemical composition. These differences are known to affect deposition, movement, and clearance from the body and carcinogenic potency. Fiber diameter is the most important factor affecting penetration and deposition in the lungs. Thin fibers have the greatest inhalation potential and deposit deep within the lungs. Fiber length, surface chemistry, and other properties affect biological activity. Fibers longer than 8 μm with a diameter of less than 1.5 μm are the most potent carcinogens (IPCS 1986).

Asbestos is released to the environment from both natural and anthropogenic sources and has been detected in indoor and outdoor air, soil, drinking water, food, and medicines. Because asbestos products were used so widely, the entire U.S. population potentially is exposed to some degree; however, the potential for exposure continues to decline, because asbestos mining has stopped, and asbestos products are

being eliminated from the market. Releases from asbestos materials in buildings and vehicle brake linings account for substantial emissions of asbestos into the air. Demolition of buildings with asbestos insulation or fireproofing may cause high atmospheric concentrations for relatively short periods. Environmental asbestos concentrations vary widely; therefore, it is not possible to accurately calculate human exposure levels except on a site-by-site basis. People may be exposed to higher-than-average levels of asbestos in air if they live near asbestos-containing waste sites or asbestos-related industries, if they use asbestos-containing products, or if they live or work in buildings with deteriorating asbestos insulation or that have undergone poorly performed asbestos removal (ATSDR 2001). In the past, families of asbestos workers potentially were exposed to high fiber levels from contaminated clothing brought home for laundering. People living in households with asbestos workers were found to have significantly elevated lung burdens of asbestos, often in the same range as found in individuals occupationally exposed to asbestos, such as shipyard workers. The asbestos-fiber burdens of occupants of a building containing asbestos insulation, on the other hand, were comparable to those of individuals with no known occupational exposure to asbestos (IARC 1977, Roggli and Longo 1991).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, almost all environmental releases of asbestos are to landfills. Reported releases declined about 80% from 1988 to 1997, then increased between 1998 and 2001, when 18.2 to 24.4 million pounds was released to landfills annually. Releases returned to lower levels after 2002. In 2007, 30 industrial facilities (mostly waste-management companies) reported releasing or disposing of about 10.5 million pounds of friable (readily crumbled) asbestos (TRI 2009).

In the past, occupational exposure occurred primarily during the mining and milling of asbestos, during the manufacture of all asbestos products, and in the construction and shipbuilding industries. Occupational exposure still occurs among workers who use asbestos end products, such as asbestos insulation workers, brake repair and maintenance workers, building demolition workers, and asbestos abatement workers (IARC 1977, ATSDR 2001, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 215,265 workers, including 9,727 women, potentially were exposed to asbestos and that 92,033 workers, including 13,262 women, potentially were exposed to chrysotile (NIOSH 1990). In 1990, the U.S. Occupational Safety and Health Administration estimated that about 568,000 workers in production and services industries and 114,000 workers in construction industries potentially were exposed to asbestos (ATSDR 2001). No more recent occupational exposure estimates were found.

Regulations

Consumer Product Safety Commission (CPSC)

Consumer patching compounds containing intentionally added respirable, free-form asbestos are banned.

Artificial emberizing materials (ash and embers) containing respirable free-form asbestos are banned.

General-use garments containing asbestos (other than those needed for personal protection and constructed so that asbestos fibers will not become airborne) are banned.

Certain household products containing intentionally added asbestos that release asbestos fibers are subject to cautionary labeling requirements.

Department of Transportation (DOT)

Asbestos is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 7 million fibers per liter.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 7 million fibers per liter for fibers longer than 10 µm.

Toxic Substances Control Act

Rules have been established for identifying, analyzing, and disposing of asbestos found in schools, and prohibitions on the manufacturing and import of asbestos products have been established.

Mine Safety and Health Administration

Permissible exposure limit (PEL) for miners (surface and underground coal, metal, and nonmetal mines): Full-shift limit = 0.1 fiber/cm^3 (8-h time-weighted average); excursion limit = 1 fiber/cm^3 (30-min sample).

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Ceiling concentration = 1 fiber/cm^3 (excursion limit) as averaged over a sampling period of 30 min.

Permissible exposure limit (PEL) = 0.1 fiber/cm^3 for fibers longer than 5 µm having a length-to-diameter ratio of at least 3 to 1.

Comprehensive standards for occupational exposure to asbestos have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 respirable fiber/cc (cm^3).

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

Recommended exposure limit (REL) = 0.1 fiber/cm^3 (fibers longer than 5 µm).

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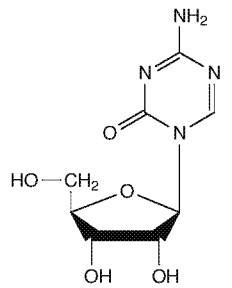
Azacitidine

CAS No. 320-67-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 5-azacytidine, 5-azaC, or Vidaza (a registered trademark of Celgene Corporation)



Carcinogenicity

Azacitidine *is reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to azacitidine by injection caused tumors at several different tissue sites in mice and rats. Intraperitoneal injection of azacitidine caused cancer of the hematopoietic system (lymphocytic or histiocytic lymphoma or granulocytic leukemia or sarcoma) in female mice and skin and lung tumors in mice of both sexes. Prenatal exposure of mice to azacitidine caused leukemia, lymphoma, and tumors of the lung and liver (NCI 1978, Luz and Murray 1988, IARC 1990). In male rats, intraperitoneal injection of azacitidine caused skin cancer (squamous-cell carcinoma) and tumors of the testis (interstitial-cell neoplasia) (IARC 1990).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to azacitidine.

Studies on Mechanisms of Carcinogenesis

In an initiation-promotion study, partially hepatectomized male rats were administered *N*-nitrosodiethylamine followed by chronic administration of azacitidine by intraperitoneal injection. The incidence of liver tumors and the combined incidence of skin and lung tumors were increased; all surviving rats developed hyperplastic liver nodules (Carr *et al.* 1988, IARC 1990).

Azacitidine in the absence of mammalian metabolic activation is genotoxic in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* test systems. It caused DNA damage and base-pair substitution mutations (but not frame-shift mutations) in prokaryotic systems and mitotic recombination, gene conversion, chromosomal aberrations, and gene mutations in somatic and germ cells of lower eukaryotes (yeast, fruit flies, and plants). In cultured rodent cells, azacitidine inhibited DNA synthesis and caused sister chromatid exchange, chromosomal aberrations, gene mutations (in some but not all studies), and morphological cell transformation. In cultured human cells, azacitidine caused DNA damage and gene mutations; studies on sister chromatid exchange and chromosomal aberrations gave conflicting results. Azacitidine did not cause dominant lethal mutations in male mice exposed *in vivo* (IARC 1990).

The carcinogenic or tumor-enhancing activity of azacitidine has been postulated to result directly or indirectly from its ability to inhibit DNA methylation (Harrison *et al.* 1983, Riggs and Jones 1983, Kerbel *et al.* 1984, 1986, Takenaga 1986, Glover and Leyland-Jones 1987, Glover *et al.* 1987, IARC 1990, Jones and Buckley 1990, Haaf 1995). Altered levels of DNA methylation can affect gene expression (Cedar 1988, IARC 1990, Fajkus *et al.* 1992, Velge *et al.* 1995), and hypomethylation is associated with the expression of genes that are normally silent or downregulated. DNA hypomethylation is somatically heritable, causing alterations in gene expression that are maintained in daughter cells as the affected cells proliferate (Holliday 2006). In pBOR-Il-3 mice, which are transgenic for the interleukin-3 (IL-3) gene (expression of which is driven by a long-terminal repeat), injection of azacitidine increased the incidence of thymic lymphoma over that observed in nontransgenic controls. The authors concluded that increased expression of IL-3, resulting from demethylation of the transgene long-terminal repeat by azacitidine, was responsible for the increased incidence of lymphoma (Saavedra *et al.* 1996). There is no evidence to suggest that the mechanisms by which azacitidine causes tumors in experimental animals would not also operate in humans.

Properties

Azacitidine is a pyrimidine analogue of cytidine that exists at room temperature as a white crystalline powder (IARC 1990). It is soluble in warm and cold water, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide, 35% ethanol, and dimethyl sulfoxide, and slightly soluble in acetone, chloroform, and hexane. Azacitidine is stable under normal temperatures and pressures (Akron 2009), but is very unstable in aqueous solution, breaking down to complex products within hours (IARC 1990). Its stability in aqueous solutions depends on pH; in neutral and alkaline solutions, it has a half-life of 4 hours, but in Ringer's solution (pH 6.2), its half-life is 65 hours (Glover and Leyland-Jones 1987). Physical and chemical properties of azacitidine are listed in the following table.

Property	Information
Molecular weight	244.2[a]
Melting point	228°C to 230°C (decomposes)[a]
Log K_{ow}	−3.83[b]
Water solubility	89 g/L at 25°C[b]
Vapor pressure	4.1×10^{-12} mm Hg at 25°C[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Azacitidine is a cytostatic anticancer drug that has been used in the United States since 1970. (NCI 1978). One product containing azacitidine as the active ingredient has been approved by the U.S. Food and Drug Administration; it is available in 100-mg vials for subcutaneous injection (FDA 2009). Azacitidine is approved to treat chronic myelomonocytic leukemia and myelodysplastic syndromes. It is also used to treat acute myeloblastic leukemia, breast cancer, colon cancer, melanoma, and ovarian cancer (IARC 1990, Santini *et al.* 2001, Celgene 2010). Azacitidine is also used in clinical trials in combina-

tion with other antineoplastic agents, such as vincristine, prednisone, vinblastine, cytarabine, or amsacrine (IARC 1990).

Production

Azacitidine may be produced synthetically or isolated from the bacterium *Streptoverticillium ladakanus* (IARC 1990). In 2009, azacitidine was available from 22 suppliers worldwide, including 15 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of azacitidine were found.

Exposure

The primary route of human exposure to azacitidine is intravenous or intramuscular injection in patients receiving anticancer therapy. Daily doses are 40 to 750 mg/m^2 of body surface. The typical treatment regimen starts with a dose of 75 mg/m^2 daily for one week of every four-week period (IARC 1990, Riley and DeRuiter 2005); the dose may be increased to 100 mg/m^2 as needed and if side effects are tolerable. In 2009, 80 clinical trials using azacitidine (alone or in combination with other drugs) for treatment of several types of cancer were in progress or recently completed (ClinicalTrials 2009). Occupational exposure could occur among health professionals and support staff (including custodians) by dermal contact, inhalation, or accidental ingestion during drug preparation or administration or cleanup of medical waste, including disposal of excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,069 health-services workers, including 698 women, potentially were exposed to azacitidine (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Azicitidine is regulated as a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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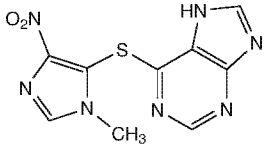
Azathioprine

CAS No. 446-86-6

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Azathioprine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Two large prospective epidemiological studies reported high incidences of non-Hodgkin's lymphoma, skin cancer (squamous-cell carcinoma), connective-tissue tumors (mesenchymal tumors), and cancer of the liver, bile ducts, or gallbladder (hepatobiliary carcinoma) in kidney-transplant patients, who are treated almost routinely with azathioprine and prednisone. Other patients treated with azathioprine (e.g., patients with rheumatoid arthritis, systemic lupus and other collagen disorders, inflammatory bowel disease, and certain skin and renal diseases) also had an increased, although lower,

risk of the same cancers as seen in the transplant patients. Rheumatoid arthritis is also a risk factor for non-Hodgkin's lymphoma (IARC 1981, 1982, 1987).

Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of azathioprine from studies in experimental animals is limited. Cancer of the ear duct (squamous-cell carcinoma) was observed in rats orally exposed to azathioprine, and lymphoma was observed in mice exposed to azathioprine by intraperitoneal, subcutaneous, or intramuscular injection. The International Agency for Research on Cancer (IARC 1981, 1982, 1987) considered these results to be inconclusive because of limitations in the study designs and inadequate reporting of these studies.

Properties

Azathioprine is a purine analogue and antimetabolite (an inhibitor of purine synthesis) that exists as pale-yellow crystals at room temperature. It is insoluble in water, very slightly soluble in ethanol and chloroform, sparingly soluble in dilute mineral acids, and soluble in dilute alkaline solutions. It is sensitive to oxidation and decomposes in strong alkali solutions (IARC 1981). Physical and chemical properties of azathioprine are listed in the following table.

Property	Information
Molecular weight	277.3[a]
Melting point	decomposes at 243°C to 244°C[a]
Log K_{ow}	0.1[a]
Water solubility	0.272 g/L at 25°C[b]
Vapor pressure	2.41×10^{-12} mm Hg at 25°C[b]
Dissociation constant (pK_a)	8.2[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Azathioprine is an immunosuppressive agent, generally used in combination with a corticosteroid to prevent rejection following allogeneic kidney transplants (i.e., from genetically different donors) and to manage severe cases of rheumatoid arthritis in adults when other treatments have failed. It may also be used following transplantation of other organs and as a second-line treatment for a variety of immunological diseases, such as systemic lupus erythematosus, autoimmune hemolytic anemia, chronic active hepatitis, ulcerative colitis, Crohn's disease, and myasthenia gravis (IARC 1981, IPCS 1996, HSDB 2009).

Production

Azathioprine was first produced commercially in the United States in 1970 and was manufactured by one U.S. company (IARC 1981). In 2009, no U.S. producers of azathioprine were identified (SRI 2009), but it was available from at least nine U.S. suppliers (ChemSources 2009), and five U.S. pharmaceutical companies produced drugs approved by the U.S. Food and Drug Administration containing azathioprine as the active ingredient (FDA 2009). No data on U.S. imports or exports of azathioprine were found.

Exposure

The routes of exposure to azathioprine during medical treatment are ingestion and intravenous injection. Kidney-transplant patients and adults with severe cases of rheumatoid arthritis or other immunological diseases may be treated with azathioprine (IARC 1981). Azathioprine is available in 25-, 50-, 75-, and 100-mg tablets and in injectable form as the sodium salt in 100-mg vials (FDA 2009). The usual dose is 3 to 5 mg/kg of body weight daily for kidney transplant patients, which may be reduced to 1 to 3 mg/kg for maintenance. For rheumatoid arthritis, the initial dose is 1 mg/kg per day, and the dose may be increased to 2.5 mg/kg per day (RxList 2009). In 2008, sales of generic forms of azathioprine totaled $53 million (Drug Topics 2009a). Azathioprine was not among the 200 most-prescribed generic drugs in 2008 (Drug Topics 2009b).

Occupational exposure to azathioprine may occur via inhalation of dust during its manufacture, formulation, and packaging. In a study at a pharmaceutical plant in South Africa, the highest median concentrations of azathioprine dust measured were 0.26 mg/m^3 in the breathing zone and 0.07 mg/m^3 in personal air samples (Jeebhay *et al.* 1993). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,849 workers, including 880 women, potentially were exposed to azathioprine (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Azathioprine is a prescription drug subject to labeling and other requirements.

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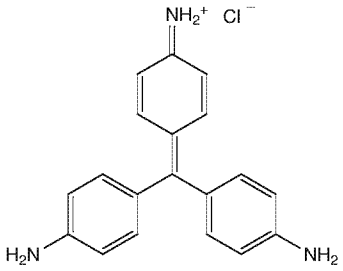
Basic Red 9 Monohydrochloride

CAS No. 569-61-9

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as C.I. basic red monohydrochloride, C.I. 42500, or pararosaniline hydrochloride



Carcinogenicity

Basic red 9 monohydrochloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to basic red 9 monohydrochloride caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral administration of basic red 9 monohydrochloride caused liver cancer (hepatocellular carcinoma) in mice of both sexes and in male rats. In rats of both sexes, it caused cancer of the Zymbal gland (carcinoma), benign and malignant thyroid-gland tumors (follicular-cell adenoma and carcinoma), and benign skin tumors (fibroma). It also caused benign and malignant skin tumors (sebaceous adenoma, trichoepithelioma, and squamous-cell carcinoma) in male rats and benign adrenal-gland tumors (pheochromocytoma) in female mice. Other tumors possibly resulting from oral exposure were mammary-gland tumors in female rats and tumors of the hematopoietic system in female mice. Subcutaneous injection of basic red 9 monohydrochloride caused cancer at the injection site (sarcoma) in rats of unspecified sex (IARC 1974, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to basic red 9 monohydrochloride. Evidence for the possible carcinogenicity of basic red 9 monohydrochloride in humans comes from an epidemiological study in which the incidence of urinary-bladder tumors was elevated among workers involved in the manufacture of magenta dye, of which basic red 9 monohydrochloride is a component (IARC 1974). However, it is not possible to determine whether the increased incidence of cancer in magenta workers was attributable to exposure to magenta or to one or more of its intermediates and impurities, such as *o*-toluidine or aniline.

Since basic red 9 monohydrochloride was listed in the *Fifth Annual Report on Carcinogens*, the International Agency for Research on Cancer has reaffirmed that the evidence for carcinogenicity in humans is inadequate for magenta and basic red 9 monohydrochloride and sufficient for the manufacture of magenta (Baan *et al.* 2008).

Properties

Basic red 9 monohydrochloride is a triphenylmethane dye that is a colorless to red or dark-green crystalline powder at room temperature. It is slightly soluble in water and ether and soluble in ethanol, methanol, and ethylene glycol methyl ether (HSDB 2009). It is stable under normal temperatures and pressures, but may decompose if heated (Akron 2009). Physical and chemical properties of basic red 9 monohydrochloride are listed in the following table.

Property	Information
Molecular weight	323.8[a]
Melting point	268°C to 270°C (decomposes)[a]
Log K_{ow}	0.21[a]
Water solubility	3 g/L at 25°C[b]
Vapor pressure	9.26×10^{-10} mm Hg[b]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Basic red 9 monohydrochloride can be used to make C.I. solvent blue 23 and is a component of magenta dye (C.I. 42510). The Biological Stain Commission has determined that magenta must contain at least 50% C.I. basic red 9 in order to perform satisfactorily as a component of nutrient agar used in biological testing. Basic red 9 monohydrochloride is also used as a biological stain and as a dye for textiles (silks and acrylics), leather, fur, paper, carbon paper, plastics, glass, waxes, polishes, soaps, cosmetics, drugs, toilet sanitary preparations, automobile antifreeze solutions, anodized aluminum, high-speed photoduplicating inks, photo-imaging systems, and ink-jet computer printers (NTP 1986, IARC 1993, HSDB 2009).

Production

Two U.S. companies produced over 900 kg (2,000 lb) of C.I. basic red 9 in 1972, over 450 kg (1,000 lb) in 1975, and between 1 million and 10 million pounds in 1977 (NTP 1986, HSDB 2009). In 2009, no commercial producers of basic red 9 monohydrochloride were identified worldwide; however, 14 suppliers were identified, including 12 U.S. suppliers (ChemSources 2009). In 1974, the United States imported 2,000 kg (4,410 lb) of basic red 9 (HSDB 2009); no more recent data on U.S. exports or imports were found.

Exposure

The routes of potential human exposure to basic red 9 monohydrochloride are dermal contact, inhalation, and ingestion. Laboratory personnel who use and handle basic fuchsin dye might be exposed to basic red 9 monohydrochloride (HSDB 2009). Exposure might also occur through its use in magenta used in photoduplicating inks, photo-imaging systems, and ink-jet computer printers. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 907 workers (mostly from the Food and Kindred Products and Health Services industries), including 733 women, potentially were exposed to basic red 9 monohydrochloride (NIOSH 1990).

Regulations and Guidelines

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

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Benzene

CAS No. 71-43-2

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Benzene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Case reports and case series have reported leukemia (mostly acute myelogenous leukemia, also known as acute myeloid or myelocytic leukemia) in individuals exposed to benzene. The strongest epidemiological evidence that benzene causes cancer is from several cohort studies in various industries and geographical locations, which found that occupational exposure to benzene increased the risk of mortality from leukemia (mainly acute myelogenous leukemia). Case-control studies also reported that exposure to benzene increased the risk of leukemia, but the usefulness of these studies was limited by poorly defined exposures and mixed exposure patterns (IARC 1974, 1982, 1987).

Since benzene was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, numerous epidemiological studies of benzene exposure have been published. Some studies found that the risk of leukemia increased with increasing benzene exposure; increased risk of death from leukemia was very high in the groups with the highest exposure (IPCS 1993). Savitz and Andrews (1997) reviewed 18 community-based and 16 industry-based studies of benzene exposure and suggested that the evidence supported an association between benzene exposure and leukemia in general, rather than specifically with acute myelogenous leukemia. Most studies found that benzene exposure increased the risks of total lymphatic and hematopoietic cancer, total leukemia, and specific histologic types of leukemia, including chronic lymphocytic leukemia, as well as acute myelogenous leukemia. Little evidence was found for an association between benzene exposure and multiple myeloma or non-Hodgkin's lymphoma.

Cancer Studies in Experimental Animals

Studies in experimental animals, including many published after benzene was listed in the *First Annual Report on Carcinogens*, have demonstrated that benzene causes cancer at numerous tissue sites in rodents. Oral exposure to benzene caused cancer of the Zymbal gland (carcinoma) in rats and mice of both sexes, cancer of the oral cavity (squamous-cell carcinoma) in rats of both sexes, malignant lymphoma and lung cancer (alveolar/bronchiolar carcinoma) in mice of both sexes, skin cancer (squamous-cell carcinoma) in male rats, benign tumors of the Harderian gland (adenoma) and cancer of the preputial gland (carcinoma) in male mice, and benign ovarian tumors and cancer of the mammary gland (carcinoma and carcinosarcoma) in female mice (NTP 1986, Huff *et al.* 1989). Inhalation exposure to benzene caused tumors at many tissue sites in rats and a tendency towards induction of lymphoid tumors in mice. Benzene administered by intraperitoneal injection caused benign lung tumors in male mice (IARC 1982, 1987). Dermal application of benzene caused benign skin tumors in transgenic mice carrying the v-Ha-*ras* oncogene, which increases their susceptibility to carcinogens (Blanchard *et al.* 1998, Spalding *et al.* 1999, French and Saulnier 2000). In heterozygous p53-deficient mice (with only one functional copy of the *p53* tumor-suppressor gene), benzene administered by stomach tube caused cancer (sarcoma) of head and neck, thoracic cavity, and subcutaneous tissue (French *et al.* 2001, Hulla *et al.* 2001).

Properties

Benzene is the primary aromatic compound. It exists at room temperature as a clear, colorless-to-yellow liquid with an aromatic odor. It is only slightly soluble in water, but it is miscible with alcohol, ether, chloroform, carbon disulfide, acetone, oils, carbon tetrachloride, glacial acetic acid, and most other organic solvents. Benzene is highly flammable (Akron 2009). Physical and chemical properties of benzene are listed in the following table.

Property	Information
Molecular weight	78.1
Specific gravity	0.8787 at 15°C/4°C
Melting point	5.5°C
Boiling point	80.1°C
Log K_{ow}	2.13
Water solubility	1.79 g/L at 25°C
Vapor pressure	94.8 mm Hg at 25°C
Vapor density relative to air	2.8

Source: HSDB 2009.

Use

Benzene is used primarily as a solvent in the chemical and pharmaceutical industries, as a starting material and intermediate in the synthesis of numerous chemicals, and in gasoline. As a raw material, it is used in the synthesis of ethylbenzene (used to produce styrene) (53%), cumene (used to produce phenol and acetone) (22%), cyclohexane (12%), nitrobenzene (used to produce aniline and other chemicals) (5%), detergent alkylate (linear alkylbenzene sulfonates) (3%), and chlorobenzenes and other products (5%). Benzene is used as an additive in gasoline, but it also is present naturally in gasoline, because it occurs naturally in crude oil and is a by-product of oil-refining processes. The percentage of benzene in unleaded gasoline is approximately 1% to 2% by volume (ATSDR 1997, HSDB 2009).

Production

Benzene has been produced commercially from coal since 1849 and from petroleum since 1941. Since 1959, the major U.S. source of benzene has been petroleum (IARC 1989). In 1994, benzene ranked 17th in production volume among chemicals produced in the United States. U.S. production of benzene increased from 5.4 million metric tons (12.0 billion pounds) in 1992 to 7.2 million metric tons (15.8

billion pounds) in 2002, an average increase of 2.8% per year (CEN 2003). Annual production during this period was highest in 2000, at 8.1 million metric tons (17.8 billion pounds). In 2009, 59 U.S. manufacturers (SRI 2009) and 24 U.S. suppliers of benzene were identified (ChemSources 2009). In 2002, U.S. imports of benzene totaled over 4 billion liters (1.1 billion gallons), which greatly exceeded exports of 6 million liters (1.6 million gallons). This trend continued in 2008, when 3.9 billion liters (1.03 billion gallons) was imported and 49.6 million liters (13.1 million gallons) was exported (USITC 2009).

Exposure

The primary route of human exposure to benzene is inhalation of ambient air. Benzene is present in the atmosphere both from natural sources, which include forest fires and oil seeps, and from industrial sources, which include automobile exhaust, industrial emissions, and fuel evaporation from gasoline filling stations. Benzene has been measured in outdoor air at various U.S. locations at concentrations ranging from 0.02 ppb (0.06 μg/m^3) in a rural area to 112 ppb (356 μg/m^3) in an urban area. The maximum 24-hour average concentrations of benzene reported for four U.S. cities in 2004 were 1.1 ppb (3.5 μg/m^3) for St. Louis, Missouri, 2.7 ppb (8.6 μg/m^3) for Chicago, Illinois, 2.9 ppb (9.3 μg/m^3) for Los Angeles, California, and 73.5 ppb (234.8 μg/m^3) for Houston, Texas (Clements *et al.* 2006). Exposure to benzene is highest in areas of heavy motor vehicle traffic and around gasoline filling stations. Based on an average benzene concentration of 12.5 ppb (40 μg/m^3) in the air and exposure of 1 hour per day, daily benzene intake from driving or riding in a motor vehicle is estimated to be 40 μg. Exposure is greater among people who spend significant time in motor vehicles in areas of congested traffic. In addition, pumping of gasoline can be a significant source of benzene exposure; for an individual spending 70 minutes per year pumping gasoline, daily benzene intake is estimated to be 10 μg (ATSDR 1997).

The general population can also be exposed to benzene by inhaling air containing tobacco smoke, drinking contaminated water, or eating contaminated food. About half of the total national exposure to benzene comes from cigarette smoke. The median level of benzene was 2.2 ppb (7 μg/m^3) in 185 homes without smokers and 3.3 ppb (10.5 μg/m^3) in 343 homes with one or more smokers. Amounts of benzene measured per cigarette ranged from 5.9 to 75 μg in mainstream smoke and from 345 to 653 μg in sidestream smoke. Benzene has been detected in fruits, vegetables, nuts, dairy products, eggs, and fish. In a 1992 survey of more than 50 foods, benzene concentrations in foods containing both benzoate and ascorbate food additives ranged from less than 1 to 38 ppb (< 3 to 120 μg/m^3) (ATSDR, 1997). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of benzene decreased from 34 million pounds in 1988 to 6 million pounds in 2001, when 5 million pounds was released to air and 19,000 lb to water. In 2007, 775 facilities released 6.3 million pounds of benzene (TRI 2009). Benzene levels in water in the vicinity of four manufacturing facilities using or producing benzene ranged from less than 1 to 179 ppb (< 3 to 569 μg/m^3) (ATSDR, 1997).

Occupational exposure may occur during production of benzene or use of substances containing it. In the vulcanization step of tire manufacturing, benzene was measured at concentrations of up to 27.2 mg/m^3, resulting in an estimated daily intake of 0.0045 mg/kg of body weight for workers (Durmusoglu 2007). The National Occupational Health Survey (conducted from 1972 to 1974) estimated that 147,600 U.S. workers potentially were exposed to benzene (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that about 272,000 workers, including 143,000 women, potentially were exposed to benzene (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Comprehensive regulations have been established for safe transport of benzene on ships and barges.

Consumer Product Safety Commission (CPSC)

Products containing 5% or more by weight of benzene are considered hazardous and require special labeling.

Solvents for paints or other surface-coating materials containing 10% or more by weight of benzene require special packaging.

Department of Transportation (DOT)

Benzene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Comprehensive regulations have been developed to control benzene levels in gasoline and benzene emissions from motor vehicles.

Mobile Source Air Toxics: Beginning in 2011, refiners must meet an annual average gasoline benzene content standard of 0.62% by volume (vol%) on all gasoline; by 2012, a maximum benzene content of 1.3 vol% may not be exceeded.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 2.2 μg/L; based on fish or shellfish consumption only = 51 μg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of benzene = U019, F005, F024, F025, F037, F038, K085, K104, K105, K141, K142, K143, K144, K145, K147, K151, K159, K169, K171, K172.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L.

Residues of benzene used as a solvent in producing modified hop extract shall not exceed 1.0 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Acceptable peak exposure = 50 ppm (maximum duration = 10 min) for select industries.

Ceiling concentration = 25 ppm for select industries.

Permissible exposure limit (PEL) = 1 ppm; = 10 ppm for select industries.

Short-term exposure limit (STEL) = 5 ppm.

Comprehensive standards for occupational exposure to benzene have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 ppm.

Threshold limit value – short-term exposure limit (TLV-STEL) = 2.5 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 500 ppm.

Short-term exposure limit (STEL) = 1 ppm.

Recommended exposure limit (time-weighted-average workday) = 0.1 ppm.

Listed as a potential occupational carcinogen.

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Benzidine and Dyes Metabolized to Benzidine

Introduction

Benzidine was first listed in the *First Annual Report on Carcinogens* (1980), and dyes metabolized to benzidine were first listed as a class in the *Ninth Report on Carcinogens* (2000). The profiles for benzidine and dyes metabolized to benzidine, which are listed (separately) as *known to be human carcinogens*, follow this introduction.

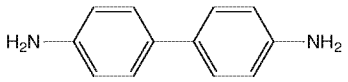
Benzidine

CAS No. 92-87-5

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as 4,4′-diaminobiphenyl



Carcinogenicity

Benzidine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous epidemiological studies (case reports and cohort studies) of workers in various geographical locations have reported a strong association between occupational exposure to benzidine and urinary-bladder cancer. Moreover, epidemiological data suggest that urinary-bladder cancer incidence has decreased since measures to limit benzidine exposure were instituted. A few studies have evaluated exposure to benzidine alone; however, in many studies, workers were co-exposed to other chemicals. Some studies have suggested that the risk of urinary-bladder cancer increases with increasing length of exposure to benzidine (IARC 1972, 1982, 1987). Since benzidine was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, some, but not all, studies have reported an association between benzidine exposure and cancer at other tissue sites (i.e., liver, kidney, central nervous system, oral cavity, larynx, esophagus, bile duct, gallbladder, stomach, and pancreas); the evidence for an association with benzidine is more limited for cancer at these tissue sites than for urinary-bladder cancer (Choudhary 1996).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of benzidine from studies in experimental animals. Oral exposure to benzidine caused mammary-gland cancer in female rats, liver cancer in mice and hamsters, and urinary-bladder cancer in dogs. When administered by subcutaneous injection, benzidine caused Zymbal-gland tumors in rats and liver tumors in mice, and when administered by intraperitoneal injection, it caused Zymbal-gland and mammary-gland tumors in rats (IARC 1982, 1987).

Studies on Mechanisms of Carcinogenesis

Benzidine is metabolized by cytochrome P450 enzymes (via N-oxidation) to form electrophilic compounds that can bind covalently to DNA (Choudhary 1996). Benzidine caused mutations in bacteria and plants, but gave conflicting results in cultured rodent

cells. It also caused many other types of genetic damage in various test systems, including yeast, cultured human and other mammalian cells, and rodents exposed *in vivo*. The damage included mitotic gene conversion (in yeast), micronucleus formation, DNA strand breaks, unscheduled DNA synthesis, cell transformation, chromosomal aberrations, sister chromatid exchange, and aneuploidy (IARC 1987). Workers exposed to benzidine and or benzidine-based dyes had higher levels of chromosomal aberrations in their white bloods cells than did unexposed workers (Choudhary 1996).

Properties

Benzidine is a biphenyl amine that exists at room temperature as a white to slightly reddish crystalline powder (ATSDR 2001). It is slightly soluble in cold water, more soluble in hot water, and readily soluble in less-polar solvents, such as diethyl ether and ethanol. It darkens on exposure to air and light (Akron 2009). Physical and chemical properties of benzidine are listed in the following table.

Property	Information
Molecular weight	184.2[a]
Specific gravity	1.250 at 20°C/4°C[a]
Melting point	120°C[a]
Boiling point	401°C[a]
Log K_{ow}	1.34[a]
Water solubility	0.322 g/L at 25°C[a]
Vapor pressure	8.98×10^{-7} mm Hg at 25°C[b]
Vapor density relative to air	6.36[a]
Dissociation constant (pK_a)	4.3[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Benzidine has been used for over a century as an intermediate in the production of azo dyes, sulfur dyes, fast color salts, naphthols, and other dyeing compounds (IARC 1982). In the past, benzidine also was used in clinical laboratories for detection of blood, as a rubber compounding agent, in the manufacture of plastic films, for detection of hydrogen peroxide in milk, and for quantitative determination of nicotine. Most of these uses have been discontinued because of concerns about benzidine's potential carcinogenicity. Some dyes that may contain benzidine as an impurity are still used as stains for microscopy and similar laboratory applications (ATSDR 2001).

Production

Benzidine is no longer manufactured for commercial sale in the United States (ATSDR 2001). All large-scale production was discontinued in 1976, and only relatively small quantities remain available for use in diagnostic testing. All benzidine production must be for captive consumption (in-house use) and take place in closed systems under stringent workplace controls. Estimated U.S. benzidine production in 1983 was only 500 lb (possibly excluding some captive production), compared with 10 million pounds in 1972 (ATSDR 2001). In 2009, no U.S. manufacturers of benzidine were identified (SRI 2009), but it was available from 13 U.S. suppliers (ChemSources 2009). Benzidine has not been imported into the United States in recent years. In 1980, the last year for which an estimate was found, U.S. imports of benzidine totaled 8,900 lb (ATSDR 2001). No data on U.S. exports of benzidine were found.

Exposure

Because benzidine may be produced only for captive consumption, its direct release into the environment is expected to be low. However, accidental releases from closed systems potentially could result in exposure of the general populaton through inhalation, ingestion, or dermal contact (ATSDR 2001). According to EPA's Toxics Release Inventory, environmental releases of benzidine were 16 lb in 1993, 250 lb in 1994, and 2 lb in 1999. Releases peaked in 2001, when 532 lb was released (300 lb to surface water and most of the rest to an offsite landfill). In 2007, two facilities released a total of 16 lb of benzidine (6 lb to air and 10 lb to a hazardous-waste landfill) (TRI 2009). In the past, benzidine might have been released into wastewaters and sludges. Because benzidine is moderately persistent in the environment, exposure of populations living near former benzidine or benzidine-dye manufacturing or waste-disposal sites may still be of concern. Benzidine has been identified in 28 of 1,585 hazardous-waste sites proposed for inclusion on the U.S. Environmental Protection Agency's National Priorities List; however, it is not known how many sites were evaluated for benzidine. In 1990, benzidine was detected in groundwater at a hazardous-waste site (the former location of a large dye manufacturer) at concentrations of 240 µg/L on site and 19 µg/L off site (ATSDR 2001).

Benzidine-based dyes may still be imported into the United States, and microbial degradation of these dyes may release free benzidine into the environment (ATSDR 2001). The U.S. Food and Drug Administration limits the benzidine content in food colorants to 1 ppb; however, other impurities in synthetic coloring agents may be metabolized to benzidine after ingestion.

Before Occupational Safety and Health Administration regulations were adopted to limit occupational exposure to benzidine (starting in 1974), benzidine and its derivatives were manufactured and used in open systems that permitted release of benzidine into workplace air. Air concentrations of benzidine measured in a benzidine manufacturing plant ranged from 0.007 to 17.6 mg/m^3, and levels in the urine of exposed workers ranged from 1 to 112 µg/L (ATSDR 2001). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,554 workers, including 426 women, potentially were exposed to benzidine (NIOSH 1990). Benzidine is available in limited quantities for use as a research chemical and may be present as a trace impurity in stains used by medical or laboratory technicians. Others potentially exposed to benzidine include workers involved in its production in closed systems and workers at hazardous-waste sites where benzidine is present (ATSDR 2001).

Regulations

Department of Transportation (DOT)

Benzidine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.000086 µg/L; based on fish or shellfish consumption only = 0.00020 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of benzidine = U021.

Benzidine is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

The color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 may contain benzidine at maximum levels that range from 1 to 20 ppb.

The color additive Ext. D&C yellow no. 1 is banned, because there is no assurance that it will not produce benzidine from the decomposition of a subsidiary reaction product.

Mine Safety and Health Administration

To control airborne exposure, benzidine shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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Dyes Metabolized to Benzidine (Benzidine Dye Class)

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Dyes that are metabolized to benzidine are *known to be human carcinogens* based on the following evidence: (1) benzidine is known to be a human carcinogen, (2) metabolism of benzidine-based dyes results in the release of free benzidine in humans and in all experimental animal species studied, and (3) benzidine exposure from exposure to benzidine-based dyes is equivalent to exposure to equimolar doses of benzidine.

Studies on Mechanisms of Carcinogenesis

Benzidine was one of the first chemicals for which an association between occupational exposure and increased cancer risk was recognized. Industrial exposure to benzidine was first associated with urinary-bladder cancer in the early 1920s. Benzidine was listed as *known to be a human carcinogen* in the *First Annual Report on Carcinogens* (1980). The evidence supporting its listing is summarized in the profile for benzidine, above.

Benzidine was first synthesized in 1845, and the first benzidine-based dye, Congo red, was prepared in 1884. A wide spectrum of colors can be achieved by varying the dye molecules' chromophores, which are linked to benzidine by an azo linkage (–N=N–). Similar or different chromophores may be linked at each amino (NH_2) group of the benzidine molecule to form various bisazobiphenyl dyes. Regardless of the chromophore(s) involved, the azo linkages of all benzidine-based dyes are essentially chemically equivalent; easily formed, they also are easily broken by chemical or enzymatic reduction to form free benzidine and free chromophore(s). Benzidine-based dyes were shown to be metabolized to free benzidine in rats, dogs (Lynn *et al.* 1980), hamsters (Nony *et al.* 1980), and rhesus monkeys, probably by bacteria in the gastrointestinal tract (Rinde and Troll 1975). Lowry *et al.* (1980) concluded that the amount of benzidine and its metabolites detected in urine of exposed workers could not be accounted for by the minute amounts of free benzidine in the dyes to which they were exposed, and therefore that humans also metabolize benzidine-based dyes to free benzidine. Lynn *et al.* (1980) found that in rats and dogs, each benzidine-based dye studied was reduced to yield an amount of free benzidine equal to that observed following an equimolar dose of benzidine.

Cancer Studies in Experimental Animals

All three benzidine-based dyes that have been tested caused cancer in rodents after oral exposure for 13 weeks (NCI 1978, IARC 1982). C.I. direct black 38 caused liver cancer in rats and mice, mammary-gland cancer in mice, and colon and urinary-bladder cancer in rats. C.I. direct blue 6 caused liver cancer in rats, and C.I. direct brown 95 caused neoplastic nodules in the liver and one malignant liver tumor in rats. Based on these data, the International Agency for Research on Cancer (IARC 1987) concluded that there was sufficient evidence for the carcinogenicity of technical-grade C.I. direct black 38, technical-grade C.I. direct blue 6, and technical-grade C.I. direct brown 95 in experimental animals.

Cancer Studies in Humans

Because benzidine workers exposed to benzidine-based dyes typically have been co-exposed to benzidine, it has been difficult to clearly establish the carcinogenicity of benzidine-based dyes in epidemiological studies. In studies of Chinese workers who remained in the same jobs for many years, the incidence of urinary-bladder cancer was elevated in workers who had been exposed almost exclusively to benzidine-based dyes (You *et al.* 1990) and in workers exposed to both benzidine and benzidine-based dyes (Bi *et al.* 1992). However, neither report adequately documented levels of exposure to either benzidine or the dyes. IARC (1982) concluded that the epidemiological data were inadequate to evaluate the carcinogenicity of individual benzidine dyes to humans, but that taken together with the presence of benzidine in the urine of exposed workers, they provided sufficient evidence that occupational exposure to benzidine-based dyes increased the risk of cancer in humans.

Properties

All benzidine-based dyes have the characteristic diazotized benzidine nucleus (the structure of benzidine is shown in the profile above) but differ with respect to the chemical groups attached at the diazo linkages. Most of the dyes in this class contain two or three azo groups, but they can contain more. They all exist as colored powders (in a wide range of hues) at room temperature and have negligible vapor

pressures. Their water solubility varies, but it is sufficient for dyeing in aqueous solution. Benzidine-based dyes are relatively stable in air and in solution at ambient temperatures but degrade in aqueous solution at high temperatures, particularly in the presence of iron. Impurities, such as benzidine, 4-aminobiphenyl, and 2,4-diaminoazobenzene, may be present in these dyes as a result of thermal or enzymatic decomposition (NIOSH 1980). There are no rigid chemical specifications for benzidine-based dyes; therefore, their composition varies according to the shade and intensity requirements of the customer (IARC 1982). Various dyes are also mixed together to produce particular colors; therefore, the final products are more accurately described as mixtures of substances than as specific chemical compounds (NIOSH 1980).

Use

Benzidine-based dyes were used primarily to color textiles, leather, and paper products and also in the petroleum, rubber, plastics, wood, soap, fur, and hair-dye industries. About 40% was used to color paper, 25% to color textiles, 15% to color leather, and 20% for diverse applications. By the mid 1970s, most manufacturers started phasing out the use of benzidine-based dyes and replacing them with other types of dyes (NIOSH 1980). More than 300 benzidine-based dyes are listed in the *Colour Index*, including 18 commercially available in the United States. Access to these dyes for home use is no longer permitted in the United States; however, some dyes (particularly direct browns, greens, and blacks) were available as consumer products in the 1970s (ATSDR 2001).

Production

Commercial quantities of benzidine-based dyes were produced in the United States starting no later than 1914, and total U.S. production reached 14 million kilograms (31 million pounds) in 1948 (IARC 1982). In 1974, nine U.S. manufacturers produced benzidine-based dyes, but by 1979, only one manufacturer remained, producing 17 benzidine-based dyes. Domestic production was about 2.9 million kilograms (6.4 million pounds) in 1976, but dropped to about 780,000 kg (1.7 million pounds) in 1978. Direct black 38 accounted for about 48% of U.S. production in 1978, followed by direct blue 2 (12.8%) and direct green 6 (6.4%) (NIOSH 1980). As of 2009, several benzidine-based dyes still had U.S. suppliers, including direct red 28 (28 suppliers), direct black 38 (12 suppliers), direct blue 6 (5 suppliers), direct green 6 (3 suppliers), direct brown 95 (3 suppliers), direct brown 2 (1 supplier), and direct blue 2 (1 supplier) (ChemSources 2009). However, these dyes are no longer used or marketed in significant quantities in the United States (ATSDR 2001). U.S. imports of benzidine-based dyes increased from 272,000 kg (600,000 lb) in 1976 to 730,000 kg (1.6 million pounds) in 1978 (NIOSH 1980) and declined to 213,000 kg (469,000 lb) in 1979. Benzidine-based dyes may still be imported into the United States, but no data on the amounts were found (ATSDR 2001).

Exposure

The primary routes of potential exposure to benzidine-based dyes are inhalation and accidental ingestion; however, dermal absorption also can occur. The potential for exposure has declined since the late 1970s, as benzidine-based dyes were removed from both industrial and consumer markets and replaced with other types of dyes. Since 1980, use of mixtures containing benzidine at concentrations of 0.1% or more is permitted only in closed systems; all workers must observe special precautions to reduce exposure, and strict procedures must be followed to transport such materials. Nevertheless, accidental releases of these dyes could lead to some occupational and environmental exposure (IARC 1982, ATSDR 2001).

In the past, environmental exposure to benzidine-based dyes potentially occurred in the vicinity of dye and pigment plants or waste-disposal sites. According to the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009), no environmental releases of benzidine-based dyes have been reported since 1989, when 750 lb of direct black 38 was released. The National Occupational Hazard Survey (NOHS, conducted from 1972 to 1974) estimated that 79,200 workers in 63 occupations (primarily the Dye Manufacturing, Textile Dyeing, Printing, Paper, and Leather industries) potentially were exposed to benzidine-based dyes (NIOSH 1976). In a Special Occupational Hazard Review for benzidine-based dyes, the National Institute for Occupational Safety and Health identified 236 benzidine-based dyes and stated that occupational exposure to such dyes had decreased since the NOHS. Of the benzidine-based dyes specifically mentioned in this profile, four (direct blue 6 tetrasodium salt and the disodium salts of direct black 38, direct brown 95, and direct red 28) were included in the National Occupational Exposure Survey (conducted from 1981 to 1983); the estimated numbers of potentially exposed workers ranged from 830 for direct brown 95 disodium salt to 11,374 for direct black 38 disodium salt (NIOSH 1990). Although no current estimate of occupational exposure to benzidine-based dyes was found, the number of potentially exposed workers is expected to be much lower than in the past.

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: C.I. direct blue 6, C.I. direct blue 218, C.I. direct black 38, and C.I. direct brown 95 are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

Benzidine-based dyes are considered potential occupational carcinogens, and it is recommended that worker exposure be reduced to the lowest feasible level.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Benzidine-based dyes are considered potential occupational carcinogens, and it is recommended that worker exposure be reduced to the lowest feasible level.

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You XY, Chen JG, Hu YN. 1990. Studies on the relation between bladder cancer and benzidine or its derived dyes in Shanghai. *Br J Ind Med* 47(8): 544-552.

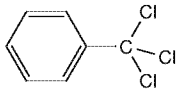
Benzotrichloride

CAS No. 98-07-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as 1-(trichloromethyl)benzene, α,α,α-trichlorotoluene, or benzoic trichloride



Carcinogenicity

Benzotrichloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to benzotrichloride by two routes of administration caused tumors at several different tissue sites in mice. When administered to female mice by stomach tube, benzotrichloride caused cancer of the forestomach (squamous-cell carcinoma) and of the lining of the lung (adenocarcinoma). Benzotrichloride applied to the skin of female mice caused lymphoma, cancer of the skin and lung (squamous-cell carcinoma), and cancer of the upper digestive tract (carcinoma of the lips, tongue, esophagus, and stomach) (IARC 1982a,b).

Since benzotrichloride was listed in the *Fourth Annual Report on Carcinogens,* additional studies in mice have been identified. Inhalation exposure of female mice to benzotrichloride caused benign and malignant lung and skin tumors (Yoshimura *et al.* 1986). In male and female strain A/J mice (a strain with a high spontaneous incidence of lung tumors), benzotrichloride given by intraperitoneal injection caused benign lung tumors (adenoma) (Stoner *et al.* 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to benzotrichloride. However, epidemiological data provide limited evidence that employment in the production of chlorinated toluenes, which involves potential exposure to benzotrichloride and other α-chlorinated toluenes, may increase the risk of cancer (IARC 1982a,b). The evidence includes (1) six case reports of respiratory-tract cancer in young benzoyl chloride production workers, including three nonsmokers, who potentially were exposed to benzotrichloride and (2) excess deaths from lung cancer in two cohorts of workers potentially exposed to benzotrichloride and other chlorinated toluenes (IARC 1982a,b). Subsequent studies reviewed by the International Agency for Research on Cancer (IARC 1999) have also reported excesses of respiratory-system cancer in workers with mixed exposure to benzotrichloride and other chlorinated toluenes (Sorahan *et al.* 1983, Wong *et al.* 1988, Sorahan and Cathcart 1989).

Properties

Benzotrichloride is a chlorinated aromatic hydrocarbon. At room temperature, it is a clear, colorless to yellow, oily liquid with a penetrating odor. It is practically insoluble in water, but it is soluble in diethyl ether, benzene, and ethanol (HSDB 2009). It is unstable and hydrolyzes in the presence of moisture (IARC 1982b). Physical and chemical properties of benzotrichloride are listed in the following table.

Property	Information
Molecular weight	195.5[a]
Specific gravity	1.38 at 20°C/4°C[a]
Melting point	–5°C[a]
Boiling point	221°C at 760 mm Hg[a]
Log K_{ow}	2.92[a]
Water solubility	53 mg/L at 5°C[b]
Vapor pressure	0.414 mm Hg at 25°C[a]
Vapor density relative to air	6.77[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

Benzotrichloride is used extensively as a chemical intermediate in manufacturing processes. Its most important derivative is benzoyl chloride (IARC 1999). It has also been used as a dye intermediate in the preparation of eight dyes and pigments, including five that have been produced in commercial quantities in the United States. In addition, benzotrichloride has been used to make benzotrifluoride and hydroxybenzophenone ultraviolet-light stabilizers for plastics and in the production of ion-exchange resins, pharmaceuticals, and antimicrobial agents (IARC 1982b).

Production

In 2009, benzotrichloride was produced by 16 manufacturers worldwide (7 in India, 4 in Europe, 3 in China, 2 in East Asia, and none in the United States) (SRI 2009) and was available from 251 suppliers, including 14 U.S. suppliers (ChemSources 2009). U.S. imports of benzotrichloride were reported in a combined category with benzyl chloride. Imports in this category were between 562,000 and 1.2 million kilograms (1.2 million and 2.7 million pounds) from 1989 to 1997, increasing to a peak of 6.2 million kilograms (13.7 million pounds) in 2001 and declining to 3.2 million kilograms (7.1 million pounds) in 2004. During this period, U.S. exports of benzotrichloride were reported in the large category of "halogenated derivatives of aromatic hydrocarbons, not elsewhere specified or included" and ranged from a high of 65 million kilograms (144 million pounds) in 1996 to a low of 20 million kilograms (44 million pounds) in 2001 (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of benzotrichloride between 1986 and 2006 ranged from 10 million to 50 million pounds (EPA 2004, 2009).

Exposure

The routes of potential human exposure to benzotrichloride are inhalation, ingestion, and dermal contact. The potential for exposure of the general population to benzotrichloride from industrial releases is expected to be low, because the chemical hydrolyzes rapidly in the presence of moisture and is degraded in the vapor phase in the at-

mosphere by reaction with photochemically produced hydroxyl radicals (IARC 1982b, HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of benzotrichloride in 1988 totaled 35,000 lb, of which 25,000 lb was released to air and 10,000 lb to off-site nonhazardous-waste landfills. Releases have since declined steadily and significantly. Since 2002, the small quantity of benzotrichloride not emitted to air (< 20 lb) has been sent to hazardous-waste landfills. In 2003, six facilities released 1,200 lb of benzotrichloride to air (TRI 2009). Benzotrichloride has been identified in surface waters at unreported concentrations (IARC 1982b).

Occupational exposure can occur if benzotrichloride is released in the work environment in liquid or vapor form during its manufacture or use as a chemical intermediate. Workers could potentially be exposed during the production, formulation, packaging, or application of products made with benzotrichloride or benzoyl chloride. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 171 male workers potentially were exposed to benzotrichloride (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Benzotrichloride is considered a hazardous material and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of substance is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.
Threshold planning quantity (TPQ) = 100 lb.
Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of benzotrichloride = U023, K015, K149.
Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – ceiling (TLV-C) = 0.1 ppm.

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Beryllium and Beryllium Compounds

CAS No. 7440-41-7 (Beryllium)

No separate CAS No. assigned for beryllium compounds as a class

Known to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as Be

Carcinogenicity

Beryllium and beryllium compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans. Beryllium and beryllium compounds were first listed in the *Second Annual Report on Carcinogens* as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be human carcinogens* in the *Tenth Report on Carcinogens* in 2002.

Cancer Studies in Humans

Epidemiological studies indicate an increased risk of lung cancer in occupational groups exposed to beryllium or beryllium compounds (Steenland and Ward 1991, Ward *et al.* 1992), supporting the conclusion that beryllium and beryllium compounds are carcinogenic in humans. An association with lung cancer has consistently been observed in several occupational populations exposed to beryllium or beryllium compounds, with a relative risk of 1.2 to 1.6. Groups with greater exposure or longer time since first exposure show higher risks, which supports a cause-and-effect relationship. Acute beryllium pneumonitis, which is a marker for high exposure to beryllium, is associated with higher lung-cancer rates (with a relative risk as high as 2.3) (Steenland and Ward 1991). Although smoking could be a factor in the cancers observed in these studies, no evidence was found in any of the published epidemiological studies to indicate a difference in smoking habits between the groups of workers exposed to beryllium or beryllium compounds and the non-exposed workers in the control groups.

Cancer Studies in Experimental Animals

Beryllium and/or beryllium compounds caused tumors in several species of experimental animals, at two different tissue sites, and by several different routes of exposure. Beryllium metal and several beryllium compounds, including beryllium-aluminum alloy, beryl ore, beryllium chloride, beryllium hydroxide, beryllium sulfate tetrahy-

drate, and beryllium oxide, caused lung tumors in rats exposed by either inhalation for one hour or a single intratracheal instillation. Inhalation exposure to beryllium metal also caused lung tumors in $p53^{+/-}$ transgenic mice (a strain with increased susceptibility to carcinogen-induced cancer). In rhesus monkeys, lung cancer was observed following inhalation exposure to beryllium sulfate (anaplastic carcinoma) or intrabronchial implantation of beryllium oxide. Bone cancer (osteosarcoma) was observed in rabbits exposed to beryllium metal, beryllium carbonate, beryllium oxide, beryllium phosphate, beryllium silicate, or zinc beryllium silicate by intravenous injection or implantation into the bone (IARC 1993, Finch *et al.* 1996, 1998)

Studies on Mechanisms of Carcinogenesis

Beryllium compounds did not cause mutations in *Salmonella typhimurium,* but they did cause genetic damage in various cultured rodent cells (IARC 1993). The genotoxic effects of beryllium compounds may result from binding of ionic beryllium to nucleic acids, which can cause infidelity of DNA replication (Leonard and Lauwerys 1987).

Properties

Beryllium is a silver-gray to grayish-white group II metallic element with an atomic weight of 9.01, melting point of 1,287°C, boiling point of 2,970°C, and density of 1.85 at 20°C. It has a close-packed hexagonal crystal structure and has several unique chemical properties. It is the lightest of all solid and chemically stable substances and has a very high melting point, specific heat, heat of fusion, and strength-to-weight ratio. Beryllium is lighter than aluminum, but it is over 40% more rigid and approximately one-third more elastic than steel. It is insoluble in water but soluble in acids and alkalis. It has excellent electrical and thermal conductivity and is not magnetic. At ordinary temperatures, beryllium resists oxidation in air; however, a thin film of beryllium oxide forms on the surface, making it highly resistant to corrosion. In alloys, beryllium contributes hardness, strength, and high electrical and thermal conductivity and enhances resistance to corrosion, wear, and fatigue (IPCS 1990, IARC 1993, HSDB 2009).

Beryllium chloride occurs as white-to-colorless deliquescent crystals. It is highly soluble in water, alcohol, benzene, ether, chloroform, and carbon disulfide, and insoluble in ammonia and acetone. Beryllium fluoride occurs as a colorless amorphous mass that is readily soluble in water but only slightly soluble in alcohol. Beryllium hydroxide exists in three forms: a metastable tetragonal crystalline solid, a stable orthorhombic crystalline solid, and a slimy, gelatinous substance with a slightly basic pH. It is insoluble in water but soluble in acids and alkalis. Beryllium oxide occurs as a white powder or gel that is insoluble in hot water and soluble in acids, alkalis, and ammonium carbonate. Beryllium metaphosphate is a white porous powder or granular material that is insoluble in water. Beryllium orthophosphate is soluble in water and acetic acid. Beryllium sulfate occurs as colorless crystals; it is insoluble in cold water and alcohol but decomposes in hot water. Beryllium sulfate tetrahydrate occurs as colorless crystals that are soluble in water, practically insoluble in ethanol, and slightly soluble in concentrated sulfuric acid (IARC 1993, ATSDR 2002).

Beryl ore occurs as colorless, blue-green, yellow, or white transparent hexagonal crystals that are insoluble in acid. Beryllium-copper alloy usually contains 4.0% to 4.25% beryllium by weight. It has a melting point of 870°C to 980°C and produces toxic fumes of beryllium oxide upon heating. Beryllium-aluminum alloy may contain 20% to 60% beryllium (IARC 1993, ATSDR 2002).

Use

Beryllium's unique properties (as a light metal with a very high melting point) make it very useful in industry. In alloys, it increases thermal and electrical conductivity and strength; addition of just 2% beryllium to copper forms alloys that are six times stronger than copper alone (IARC 1993). A 2010 U.S. Geological Survey Mineral Commodities Survey reported that based on sales revenues, nearly half of beryllium use was in computer and telecommunications products, and the remainder was in aerospace and defense applications, appliances, automotive electronics, industrial components, and other applications (Jaskula 2010).

Pure beryllium metal is used in aircraft disc brakes, X-ray transmission windows, space vehicle optics and instruments, aircraft and satellite structures, missile parts, nuclear reactor neutron reflectors, nuclear weapons, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, mirrors, high-speed computers, and audio components. Beryllium alloyed with copper, aluminum, or other metals is used in the electronics, automotive, defense, and aerospace industries. More specifically, beryllium alloys are used in electrical connectors and relays, springs, precision instruments, aircraft engine parts, nonsparking tools, submarine cable housings and pivots, wheels, pinions, automotive electronics, molds for injection-molded plastics, telecommunications devices, computers, home appliances, dental applications, golf clubs, bicycle frames, and many other applications (IPCS 1990, IARC 1993, ATSDR 2002, HSS 2009). Beryllium-copper alloy is used in a wide variety of applications, including electrical connectors and relays, wheels and pinions, nonsparking tools, and switches in automobiles (ATSDR 2002). Beryllium–aluminum alloy has been used in light aircraft construction (Merian 1984). It also may be used in casting alloys, where it refines the grain size, resulting in better surface polishing, reduces melt losses, and improves casting fluidity (IARC 1980, Kaczynski 2002).

Beryllium oxide is the most important high-purity commercial beryllium chemical produced (Kaczynski 2000). It is used in high-technology ceramics, electronic heat sinks, electrical insulators, microwave oven components, gyroscopes, military vehicle armor, rocket nozzles, crucibles, nuclear reactor fuels, thermocouple tubing, laser structural components, substrates for high-density electrical circuits, and automotive ignition systems, and as an additive to glass, ceramics, and plastics (IARC 1993, ATSDR 2002). Beryllium oxide also is used in the preparation of beryllium compounds, as a catalyst for organic reactions, and in high-temperature reactor systems. Beryllium oxide was used in the past in the manufacture of phosphors for fluorescent lamps.

Beryllium chloride is used primarily to manufacture beryllium metal by electrolysis in the laboratory. It also is used as an acid catalyst in organic reactions. Beryllium fluoride and beryllium hydroxide are used commercially in the production of beryllium metal and beryllium alloys, and beryllium fluoride is used in the manufacture of glass and nuclear reactors (Sax and Lewis 1987). Beryllium sulfate is used primarily for the production of beryllium oxide powder for ceramics, and beryllium nitrate is used as a chemical reagent and for stiffening mantles in gas and acetylene lamps (HSDB 2009). The primary use of beryllium sulfate tetrahydrate is as a chemical intermediate in the processing of beryl and bertrandite ores (Sax and Lewis 1987). Beryllium metaphosphate has limited use as a raw material in special ceramic compositions and as a catalyst carrier. Beryllium zinc sulfate was formerly used as an oxygen-dominated phosphor in luminescent materials (IARC 1980, Sax and Lewis 1987).

Production

Beryllium was discovered in 1798, but it did not become commercially important until the 1930s. Although more than 40 beryllium-bearing minerals are known, only two (beryl and bertrandite) currently are commercially important. Beryl ($3BeO{\cdot}Al_2O_3{\cdot}6SiO_2$), which contains

approximately 11% beryllium oxide (up to 4% beryllium), is the predominant beryllium-containing mineral mined. Beryl is found largely in Brazil and the former Soviet Union. Impurities in beryl include alkali metals, alkaline-earth metals, iron, manganese, and phosphorus. Emeralds (beryl containing chromium), aquamarine (beryl containing iron), and other semiprecious gems are examples of beryl at its purest gem quality (IARC 1993, Jaskula 2009).

U.S. companies have produced beryllium and some beryllium compounds commercially since the 1940s and beryllium oxide since 1958 (IARC 1972). Bertrandite ($4BeO{\cdot}2SiO_2{\cdot}H_2O$) is the principal beryllium-containing mineral mined in the United States; it contains less than 1% beryllium, but it can be efficiently processed into beryllium hydroxide (IARC 1993). The Topaz-Spor Mountain area of Utah is currently being mined for beryllium; it contains a large reserve of bertrandite, totaling about 15,800 metric tons (35 million pounds) of beryllium (Jaskula 2009). The United States is the world's largest producer of beryllium, accounting for roughly 86% of world production in 2009; total U.S. production was 120 metric tons (265,000 lb), down from 176 metric tons (388,000 lb) in 2008. Other countries producing beryllium (in order of amount produced in 2007) are China, Mozambique, Portugal, Madagascar, and Brazil (Jaskula 2009, 2010).

In 2009, U.S. beryllium consumption, imports, exports, and government stockpile releases were considerably lower than in each of the previous four years (Jaskula 2010). Consumption was 140 metric tons (309,000 lb), down from 220 metric tons (485,000 lb) in 2008; imports for production were 20 metric tons (44,000 lb), down from 70 metric tons (154,000 lb); exports were 30 metric tons (66,000 lb), down from 112 metric tons (247,000 lb); and government stockpile releases were 11 metric tons (24,000 lb), down from 39 metric tons (86,000 lb). In 2009, one U.S. producer of beryllium oxide and one U.S. producer of beryllium sulfate were identified, but no U.S. producers of beryllium nitrate (SRI 2009). U.S. suppliers identified in 2009 included 2 for beryllium, 16 for beryllium oxide, 1 for beryllium hydroxide, 4 for beryllium sulfate, 9 for beryllium sulfate tetrahydrate, 4 for beryllium chloride, 5 for beryllium fluoride, and 2 for beryllium copper alloy (ChemSources 2009).

Natural sources of beryllium and beryllium compounds in the atmosphere (annual amounts) are windblown dust (5 metric tons, or 11,000 lb) and volcanic particles (0.2 metric tons, or 441 lb). Anthropogenic sources include electric utilities (3.5 metric tons, or 7,716 lb), industry (0.6 metric tons, or 1,323 lb), metal mining (0.2 metric tons, or 441 lb), and waste and solvent recovery (0.007 metric tons, or 15 lb) (ATSDR 2002).

Exposure

The primary route of human exposure to beryllium is through inhalation of dusts and fumes (ATSDR 2002). Beryllium may also be ingested in drinking water or food. Beryllium was measured in fruit and fruit juices at concentrations ranging from less than 0.1 μg/L in a pineapple to 74.9 μg/L in a papaya. Cigarettes contain beryllium at concentrations of up to 0.0005 μg per cigarette. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, 2007 environmental releases totaled 14,185 lb of beryllium from 12 facilities and 862,894 lb of beryllium compounds from 61 facilities (TRI 2009). In measurements at 100 U.S. locations, the average daily beryllium concentration in air was less than 0.0005 $\mu g/m^3$. Beryllium was detected at 2,760 of 50,000 U.S. surface-water sites, at an average concentration of 1.9 μg/L, and at 30 of 334 groundwater sites, at an average concentration of 1.7 μg/L. Beryllium occurs naturally in soils at concentrations ranging from less than 1 to 15 mg/kg. The average daily inhalation exposure to beryllium for a U.S. adult was estimated at less than 0.0006 μg, and the average daily exposure from food was estimated at 0.12 μg (ATSDR 2002).

The highest levels of human exposure to beryllium are through occupational exposure, which may occur through inhalation of beryllium dust or dermal contact with products containing beryllium. Workers with the highest potential for exposure include beryllium miners, beryllium alloy makers and fabricators, phosphorus manufacturers, ceramics workers, missile technicians, nuclear reactor workers, electric and electronic equipment workers, and jewelers. Occupational exposure may also lead to at-home exposure to beryllium on work garments. In studies in the workplace, air concentrations from personal monitors mounted on clothing increased when the amount of beryllium dust on the fabric increased (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 10,510 workers potentially were exposed to beryllium (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 13,938,000 workers, including 739 women, potentially were exposed to beryllium; 4,305 workers, including 849 women, to beryllium oxide; 1,822 workers, including 230 women, to beryllium sulfate tetrahydrate; and 1,740 workers, including 37 women, to beryllium-copper alloy (NIOSH 1990).

Regulations

Department of Energy (DOE)

DOE has established the Chronic Beryllium Disease Prevention Program to protect workers from excessive beryllium exposure and beryllium disease.

Department of Transportation (DOT)

Numerous beryllium compounds and beryllium compounds not otherwise specified are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Beryllium compounds are listed as hazardous air pollutants.

Urban Air Toxics Strategy: Beryllium compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Beryllium and beryllium compounds are listed as a toxic pollutants.

Limits have been established for beryllium in biosolids (sewage sludge) when disposed of via incineration.

Beryllium chloride, beryllium fluoride, and beryllium nitrate are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for beryllium; = 1 lb for beryllium chloride, beryllium fluoride, beryllium nitrate.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Beryllium and beryllium compounds are listed substances subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of beryllium powder = P015.

Beryllium powder and beryllium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.004 mg/L for beryllium.

Food and Drug Administration (FDA)

Maximum permissible level of beryllium in bottled water = 0.004 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Acceptable peak exposure = 0.025 mg/m^3 (30-min maximum duration per 8-h shift) for beryllium and beryllium compounds (as Be).

Ceiling concentration = 0.005 mg/m^3 for beryllium and beryllium compounds (as Be).

Permissible exposure limit (PEL) = 0.002 mg/m^3 for beryllium and beryllium compounds (as Be).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.00005 mg/m^3 for beryllium and beryllium compounds (as Be).

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 4 mg/m^3 for beryllium and beryllium compounds (as Be).

Beryllium and beryllium compounds are listed as potential occupational carcinogens.

Ceiling recommended exposure limit = 0.0005 mg/m^3 for beryllium and beryllium compounds (as Be).

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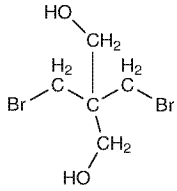
2,2-Bis(bromomethyl)-1,3-propanediol (Technical Grade)

CAS No. 3296-90-0

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as BBMP



Carcinogenicity

The flame retardant 2,2-bis(bromomethyl)-1,3-propanediol, technical grade, is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2,2-bis(bromomethyl)-1,3-propanediol (BBMP), technical grade, caused tumors at several different tissue sites in rats and mice. In two-year studies, dietary administration of BBMP caused tumors of the oral cavity, esophagus, mammary gland, and thyroid gland in rats of both sexes. In male rats, it also caused mononuclear-cell leukemia and tumors of the skin, subcutaneous tissue, Zymbal gland, forestomach, small and large intestines, mesothelium, urinary bladder, lung, and seminal vesicle. In similar studies with mice, BBMP caused tumors of the Harderian gland and lung in both sexes, the kidney in males, and the subcutaneous tissue in females (NTP 1996, Dunnick *et al.* 1997, IARC 2000). Dietary administration of BBMP for three months, followed by maintenance on a control diet for up to two years, caused tumors in male rats at the same tissue sites as in the two-year study of male rats described above. However, this study found higher incidences of tumors of the oral cavity, forestomach, small and large intestines, lung, Zymbal gland, thyroid gland, and mesothelium than did the two-year study; these tumors were considered to be related to BBMP exposure (NTP 1996, Dunnick *et al.* 1997).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to BBMP (IARC 2000).

Studies on Mechanisms of Carcinogenesis

BBMP caused mutations in *Salmonella typhimurium* strains TA100 and TA1535 only in the presence of mammalian metabolic activation (Zeiger *et al.* 1992). In cultured Chinese hamster ovary cells, BBMP caused chromosomal aberrations only in the presence of mammalian metabolic activation, and it did not cause sister chromatid exchange with or without activation. *In vivo* exposure to BBMP under various conditions induced micronucleus formation in the erythrocytes of mice (NTP 1996). There is no evidence to suggest that mechanisms by which BBMP causes tumors in experimental animals would not also operate in humans.

Properties

BBMP is a brominated alkyl (neopentyl) glycol with an aliphatic neopentyl structure that exists at room temperature as a white solid material with a mild musty odor. It is soluble in water and benzene, very

soluble in acetone, isopropanol, and methanol, and slightly soluble in carbon tetrachloride and xylenes (HSDB 2009). Physical and chemical properties of BBMP are listed in the following table.

Property	Information
Molecular weight	262.0[a]
Melting point	111°C to 113°C[a]
Log K_{ow}	2.29[a]
Water solubility	38 g/L at 25°C[b]
Vapor pressure	1.3×10^{-5} mm Hg at 25°C[b]
Dissociation constant (pK_a)	13.57[c]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009, [c]Akron 2009.

Use

BBMP is used as a flame retardant in unsaturated polyester resins, for molded products, and in the production of rigid polyurethane foam. It is also used as a chemical intermediate in the production of pentaerythritol ethers and other derivatives used as flame retardants (IARC 2000, HSDB 2009).

Production

Annual U.S. production of BBMP was estimated at over 2,300 kg (5,000 lb) in 1977 and 1979 (HSDB 2009) and at 3 million to 4 million pounds in 1983 (NTP 1996). BBMP was listed by the U.S. Environmental Protection Agency as a high-production-volume chemical in 1990, indicating that annual production exceeded 1 million pounds (EPA 2006). In 2009, BBMP was produced by one manufacturer each in the United States, Middle East, and China (SRI 2009) and was available from 14 suppliers, including 7 U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of human exposure to BBMP are inhalation and dermal contact. BBMP may enter the environment as dust and through wastewater (NTP 1996). If released to air, BBMP is expected to exist in both vapor and particulate phases. The half-life of the vapor phase is estimated to be 2 days. If released to water, BBMP is expected to be adsorbed to sediments and suspended solids and not to volatilize from the surface of the water. If released to soil, it is expected to have moderate mobility, based on a soil-water partition coefficient of 420 (HSDB 2009). Occupational exposure to BBMP may occur in industries where it is used as a flame retardant, for example, in production of unsaturated polyester resins, molded products, and rigid polyurethane foam (NTP 1996).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to BBMP were identified.

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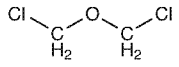
Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether

CAS Nos. 542-88-1 and 107-30-2

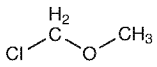
Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as BCME and CMME



Bis(chloromethyl) ether



Chloromethyl methyl ether

Carcinogenicity

Bis(chloromethyl) ether (BCME) and technical-grade chloromethyl methyl ether (CMME) are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous epidemiological studies and case reports from various geographical locations have demonstrated that occupational exposure to BCME or CMME causes lung cancer (predominantly small-cell carcinoma). The risk of lung cancer was shown to increase with increasing exposure duration or cumulative exposure. Among the most heavily exposed workers, the risk of lung cancer was increased at least tenfold, and the time between exposure and diagnosis of disease was shorter. The studies were of workers exposed either to BCME or to CMME; however, because BCME is a contaminant of technical-grade CMME (at levels of 1% to 7%), workers exposed to CMME probably were also exposed to BCME. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of BCME and technical-grade CMME in humans (IARC 1974, 1987).

Cancer Studies in Experimental Animals

Exposure to BCME by inhalation caused lung tumors in rats and mice and nasal-cavity tumors in rats. Administration of BCME by subcutaneous injection caused lung tumors in mice of both sexes and connective-tissue tumors (fibroma and/or fibrosarcoma) at the injection site in mice of both sexes and in female rats. Dermal exposure of female mice to BCME caused benign skin tumors (papilloma), most of which progressed to skin cancer (squamous-cell carcinoma). Evaluation of technical-grade CMME is complicated by the presence of BCME as a contaminant. Exposure to technical-grade CMME by inhalation caused a low incidence of respiratory-tract tumors in rats and hamsters, and subcutaneous administration caused tumors at the injection site (sarcoma) in mice. IARC (1987) concluded that there was sufficient evidence for the carcinogenicity of BCME and technical-grade CMME in experimental animals.

Studies on Mechanisms of Carcinogenesis

BCME caused mutations in bacteria. It also caused unscheduled DNA synthesis in cultured human cells but did not cause chromosomal aberrations in bone-marrow cells of rats exposed *in vivo*. CMME caused mutations in bacteria and enhanced virus-induced transformation of mammalian cells. The incidence of chromosomal aberrations was increased slightly in white blood cells from workers exposed to BCME or CMME (IARC 1987).

Properties

BCME is a chloroalkyl ether compound that exists at room temperature as a colorless liquid with a suffocating odor. It is only slightly soluble in water, but it is miscible with ethanol, ethyl ether, and many organic solvents. The compound is unstable in moist air and hydrolyzes rapidly in water (Akron 2009). Physical and chemical properties of BCME are listed in the following table. No physical or chemical properties were identified for technical-grade CMME.

Property	Information (BCME)
Molecular weight	115.0
Specific gravity	1.323 at 15°C/4°C
Melting point	–41.5°C
Boiling point	106°C
Log K_{ow}	1.04
Water solubility	1.020 g/L at 25°C
Vapor pressure	29.4 mm Hg at 25°C
Vapor density relative to air	4

Source: HSDB 2009.

Use

BCME and CMME are used primarily as chemical intermediates and alkylating agents. BCME is used as a laboratory reagent, in the manufacture of plastics, ion-exchange resins, and polymers, and as a monitoring indicator for chloromethyl ether (HSDB 2009). BCME formerly was used for cross-linking of cellulose, for surface treatment of vulcanized rubber to increase adhesion, and in the manufacture of flame-retardant fabrics (ATSDR 1989). CMME is used as an alkylating agent and industrial solvent in the manufacture of dodecylbenzyl chloride, water repellents, ion-exchange resins, and polymers, and as a chloromethylation reagent (HSDB 2009).

Production

BCME and CMME previously were manufactured in the United States, but use of these chemicals had been widely curtailed by 1976 (HSDB 2009). In 1977, U.S. production of BCME was 45,400 kg (100,000 lb), and that of CMME was 4.6 million kilograms (10 million pounds). In 1982, BCME was no longer produced in the United States, and only 2,270 kg (5,000 lb) of CMME was produced. There were three U.S. manufacturers of CMME in 1969, one in 1973, and none in 2009 (IARC 1974a,b, HSDB 2009, SRI 2009). Although BCME is no longer produced commercially in the United States, small quantities may be produced or repackaged as a chemical intermediate or laboratory chemical (ATSDR 1989, HSDB 2009). In 2009, BCME was available from five U.S. suppliers and CMME from nine U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of BCME or CMME were found.

Exposure

The primary routes of potential human exposure to BCME and technical-grade CMME are inhalation and dermal contact. Because BCME is little used in the United States and because it is rapidly degraded in the environment, the probability of human exposure is very low. BCME has not been detected in ambient air or water (ATSDR 1989).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, almost all environmental releases of BCME and CMME have been to the air. Reported annual releases of BCME to air ranged from 255 to 574 lb in the early 1990s, but since 1995, annual releases to air have not exceeded 7 lb, and no releases to air were reported in 1995, 1996, 1998, 2000, or 2009. Releases of CMME to air since 1988 (the earliest year for which reports were available) have fluctuated between 1,000 lb in 1988 and 4,155 lb in 1997. In 2009, one facility reported releases of 3,600 lb of CMME to air (TRI 2009).

The primary route of occupational exposure to BCME or CMME is inhalation of vapors; however, the potential for exposure is low, because these chemicals are no longer produced or sold in large quantities, and most industrial operations involving them take place in closed-process vessels. The most likely means of exposure to BCME is during the production or use of chemicals in which it may occur as a contaminant or may be formed inadvertently. The potential for occupational exposure to BCME or CMME is greatest for chemical plant workers, ion-exchange resin makers, laboratory workers, and polymer makers (ATSDR 1989). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 14 workers (all laboratory workers), including 5 women, potentially were exposed to BCME. No estimate of potential exposure to CMME was reported (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: BCME and CMME are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 1,000 lb for BCME and 5,000 lb for CMME.

Clean Water Act

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00010 µg/L for BCME; based on fish or shellfish consumption only = 0.00029 µg/L for BCME.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for BCME and CMME.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: BCME and CMME are listed substances subject to reporting requirements.
Threshold planning quantity (TPQ) = 100 lb for BCME and CMME.
Reportable quantity (RQ) = 10 lb for BCME and CMME.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of BCME = P016 and on the presence of CCME = U046.
BCME and CMME are listed as a hazardous constituents of waste.

Mine Safety and Health Administration

To control airborne exposure, neither BCME nor CMME shall be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

BCME and CMME are listed as a potential occupational carcinogens: Engineering controls, work practices, and personal protective equipment are required.
BCME and CMME are considered highly hazardous chemicals: Threshold quantity (TQ) = 100 lb for BCME; = 500 lb for CMME.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.001 ppm for BCME; = exposure to CCME by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

BCME and CMME are listed as potential occupational carcinogens.

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Bromodichloromethane

CAS No. 75-27-4

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Carcinogenicity

Bromodichloromethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to bromodichloromethane caused tumors at several different tissue sites in mice and rats. Administration of bromodichloromethane by stomach tube caused benign and malignant kidney tumors (tubular-cell adenoma and adenocarcinoma) in male mice and in rats of both sexes, benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female mice, and benign and malignant colon tumors (adenomatous polyps and adenocarcinoma) in rats of both sexes (NTP 1987, ATSDR 1989, IARC 1991, 1999).

Since bromodichloromethane was listed in the *Sixth Annual Report on Carcinogens*, additional studies in rats have been identified. Administration of bromodichloromethane in the drinking water increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma or carcinoma) in males (George *et al.* 2002) and caused benign liver tumors (hepatocellular adenoma) in females (Tumasonis *et al.* 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to bromodichloromethane. Several epidemiological studies indicated a possible association between ingestion of chlorinated drinking water (which typically contains bromodichloromethane) and increased risk of cancer in humans, but these studies could not provide information on whether any observed effects were due to bromodichloromethane or to one or more of the hundreds of other by-products also present in chlorinated water (ATSDR 1989).

Properties

Bromodichloromethane is a trihalomethane that exists as a colorless liquid at room temperature. It is slightly soluble in water and very soluble in ethanol, ethyl ether, benzene, and acetone. It is stable at normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties for bromodichloromethane are listed in the following table.

Property	Information
Molecular weight	163.8
Specific gravity	1.980 at 20°C/4°C
Melting point	–57°C
Boiling point	90°C
Log K_{ow}	2.00
Water solubility	3.96 g/L at 30°C
Vapor pressure	50 mm Hg at 20°C

Source: HSDB 2009.

Use

Bromodichloromethane is used in the synthesis of organic chemicals and as a reagent in laboratory research. It previously was used as a solvent for fats, waxes, and resins, and it has been used to separate minerals and salts, as a flame retardant, and as an a ingredient in fire extinguishers (ATSDR 1989).

Production

Bromodichloromethane is not used or produced commercially in the United States. Small quantities have been produced, but production volumes were not found (ATSDR 1989). In 2009, bromodichloromethane was available from 18 suppliers worldwide, including 11 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports were found, but little, if any, trade is expected (ATSDR 1989).

Exposure

Bromodichloromethane is a by-product of water disinfection, and the main route of human exposure is through exposure to chlorine-treated water (IARC 1991). The amount of bromodichloromethane produced during chlorination depends on temperature, pH, the bromide ion concentration of the water, the presence of trihalomethane precursors, and the specific treatment processes (ATSDR 1989). The organic trihalomethane precursors are naturally occurring humic and fulvic acids. The general population is exposed to trihalomethanes through consumption of treated drinking water, beverages, and food products, inhalation of contaminated air, and dermal contact with treated water.

As water-disinfection by-products, trihalomethanes occur at higher concentrations in finished water than in raw waters. It is estimated that bromodichloromethane levels increase by 30% to 100% in water distribution pipes; formation of bromodichloromethane is likely to continue as long as chlorine and organic trihalomethane precursors remain in the water (ATSDR 1989). Since 1998, the concentration of total trihalomethanes in public water systems has been limited to 80 ppb (µg/L) (EPA 1998). The highest detected concentration of bromodichloromethane before regulations went into effect was in New Orleans, Louisiana, where its concentration was 11 ppb (µg/L) in raw water and 116 ppb in finished water (NRC 1980). In the water supplies of 113 U.S. cities surveyed from 1976 to 1977, the mean bromodichloromethane concentration was 18 ppb (IARC 1991). Bromodichloromethane was detected in 445 of 945 finished water supplies from groundwater sources in a survey conducted from 1981

to 1982, at a median concentration of approximately 1.8 ppb (HSDB 2009), and in 35 of 40 Michigan water supplies at a median concentration of 2.7 ppb (Furlong and D'Itri 1986). Bromodichloromethane was found in 14 of 63 industrial wastewater discharges, at concentrations ranging from less than 10 to 100 ppb (HSDB 2009).

The tap-water uses associated with the greatest bromodichloromethane exposure, based on concentrations of total trihalomethanes in the blood or exhaled breath, were showering, bathing, and hand dishwashing (Ashley *et al.* 2005, Nuckols *et al.* 2005). Ingestion of tap water or hot or cold beverages containing tap water did not increase blood or exhaled breath concentrations. The concentration of bromodichloromethane in the blood increased 3- to 4-fold after showering; for two study sites, the median blood concentrations were 38 and 43 ppt (ng/L) after showering (Nuckols *et al.* 2005), and the median water concentrations of bromodichloromethane were 14 and 12 ppb.

Exposure can also occur from dermal contact with and ingestion of chlorinated swimming-pool water. Individuals who frequent indoor swimming pools and saunas potentially are at higher risk from inhalation exposure (ATSDR 1989). Bromodichloromethane was detected at concentrations of 13 to 34 ppb in chlorinated freshwater pools (Beech *et al.* 1980). Another study examined dermal and inhalation exposure of two college students (one male and one female) to bromodichloromethane during a typical two-hour swimming workout. The results suggested that the main route of exposure was dermal, rather than inhalation, and showed that training was associated with a measurable body burden of bromodichloromethane (Lindstrom *et al.* 1997). Another study found that concentrations of bromodichloromethane in the urine of swimming-pool workers depended on its concentration in the air in the swimming-pool enclosure and increased over the course of a four-hour shift by a factor of 2.5 (Caro and Gallego 2007). At the same pool, concentrations of bromodichloromethane in the urine of swimmers increased by a factor of 3 to 4 after one hour of exercise. Because the workers and swimmers were exposed to the same air concentration of bromodichloromethane, the difference in uptake was attributed to dermal absorption by the swimmers. These results agree with those of a similar study of swimmers that measured bromodichloromethane in alveolar air before and after swimming (Aggazzotti *et al.* 1998).

Although consumers potentially are exposed to bromodichloromethane from contaminated food, resulting from use of chlorinated water to produce these foods, such exposure is not common, and concentrations of bromodichloromethane in food are at or below concentrations in drinking water (HSDB 2009). In the U.S. Food and Drug Administration's Total Diet Study, bromodichloromethane was found in 46 food products, at concentrations ranging from 3 ppb (the limit of quantitation) to 37 ppb (FDA 2003). Bromodichloromethane was detected in cola drinks at concentrations of 2.3 to 3.8 ppb in one study (HSDB 2009); in another study, it was found in non-caramel-colored soft drinks at 0.1 to 0.2 ppb and in cola drinks at 0.9 to 5.9 ppb (Abdel-Rahman 1982).

Bromodichloromethane is not produced on a large commercial scale (HSDB 2009). If contamination occurs from a spill on land, volatilization will occur, which is the predominant environmental removal process, or the compound will leach into groundwater, where significant biodegradation can occur under anaerobic conditions. Bromodichloromethane has a relatively long half-life in air, estimated at 2 to 3 months (ATSDR 1989). Reactions with hydroxyl radicals or singlet oxygen are probably the only identifiable transformation processes in the atmosphere. Long-range global transport is possible. Bromodichloromethane has been detected in rainwater, indicating that washout from the atmosphere is possible; however, it is likely that the compound will revolatilize (HSDB 2009). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, the largest total environmental releases of bromodichloromethane occurred in 1992, when 15,000 lb was released, all as fugitive air emissions. In 2007, one industrial facility released 296 lb of bromodichloromethane to the air (TRI 2009).

The potential for occupational exposure to bromodichloromethane is greatest among workers using it as a reagent for research or to synthesize organic chemicals. Most other uses have been discontinued (ATSDR 1989). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 3,266 workers, including 502 women, potentially were exposed to bromodichloromethane (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Halomethanes are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.55 µg/L; based on fish or shellfish consumption only = 17 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.080 mg/L for total trihalomethanes (sum of chloroform, bromodichloromethane, dibromochloromethane, and bromoform).

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.08 mg/L for total trihalomethanes.

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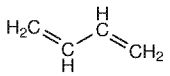
1,3-Butadiene

CAS No. 106-99-0

Known to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)



Carcinogenicity

1,3-Butadiene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. 1,3-Butadiene was first listed in the *Fifth Annual Report on Carcinogens* in 1989 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be a human carcinogen* in the *Ninth Report on Carcinogens* in 2000.

Cancer Studies in Humans

A number of epidemiological studies have shown an association between occupational exposure to 1,3-butadiene and excess mortality from cancer of the lymphatic and hematopoietic systems. These include (1) a cohort study showing increased risk of lymphosarcoma and reticulosarcoma in workers who manufactured 1,3-butadiene monomer, (2) a study of styrene-butadiene rubber workers in eight plants in the United States and Canada showing increased risk of leukemia among production workers, and (3) a case-control study within the cohort of styrene-butadiene rubber workers showing a large excess of leukemia associated with exposure to 1,3-butadiene and not to styrene (IARC 1992). In addition, an excess of lymphosarcoma and reticulosarcoma was found among 1,3-butadiene production workers in a previously unstudied chemical plant (Ward *et al.* 1996). Excess deaths from leukemia were observed among long-term workers who were hired before 1960 and had worked in the three (of eight studied) styrene-butadiene rubber plants with the highest exposure to butadiene (standardized mortality ratio = 1.8 in comparison with the U.S. population). A second case-control study of styrene-butadiene rubber workers with lymphopoietic cancer (with a new set of controls for each case) confirmed the strong association and significant dose-response relationship between 1,3-butadiene exposure score and risk of leukemia (Matanoski *et al.* 1993). Finally, a follow-up study of styrene-butadiene rubber workers in the synthetic rubber industry also found a dose-response relationship between 1,3-butadiene exposure level and the occurrence of leukemia (Delzell *et al.* 1996, 2006, Macaluso *et al.* 1996).

Studies on Mechanisms of Carcinogenesis

1,3-Butadiene appears to cause tumors in humans and rodents through its metabolism to DNA-reactive epoxide intermediates, which cause genetic alterations in proto-oncogenes or tumor-suppressor genes (Melnick and Kohn 1995). Mouse, rat, and human liver microsomes have been shown to oxidize 1,3-butadiene to epoxybutene (Csadany *et al.* 1992) and to further oxidize the monoepoxide to diepoxybutane (Seaton *et al.* 1995). These metabolites form *N*'-alkylguanine adducts that have been detected in liver DNA of mice exposed to 1,3-butadiene and in the urine of a worker exposed to 1,3-butadiene. Activated K-*ras* oncogenes and inactivated tumor-suppressor genes observed in 1,3-butadiene-induced tumors in mice are analogous to genetic alterations frequently observed in a wide variety of human cancers. Dose-related increases in *hprt* mutations have been observed in lymphocytes isolated from mice exposed to 1,3-butadiene or its epoxide metabolites and in occupationally exposed workers. The mutational spectra for 1,3-butadiene and its epoxide metabolites at the *hprt* locus in mouse lymphocytes are similar to the mutational spectrum for ethylene oxide, an alkylating agent listed in the Report on Carcinogens as *known to be a human carcinogen.*

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 1,3-butadiene from studies in experimental animals. Inhalation exposure to 1,3-butadiene caused benign or malignant tumors at several different tissue sites in rodents, including the hematopoietic system, heart (hemangiosarcoma), lung, forestomach, Harderian gland, preputial gland, liver, mammary gland, ovary, and kidney in mice (NTP 1984, Huff *et al.* 1985, Melnick *et al.* 1990) and the pancreas, testis, thyroid gland, mammary gland, uterus, and Zymbal gland in rats (Owen *et al.* 1987).

Properties

1,3-Butadiene is an olefin which at room temperature is a colorless gas with a mild aromatic or gasoline odor. It is insoluble in water but soluble in ether, ethanol, acetone, and other organic solvents. It polymerizes readily, especially in the presence of oxygen; therefore, it is shipped and stored with an inhibitor to prevent this reaction (Akron 2009). It is also a dangerous fire hazard. Physical and chemical properties of 1,3-butadiene are listed in the following table.

Property	Information
Molecular weight	54.1[a]
Density	0.6149 g/cm^3 at 25°C[a]
Melting point	–108.966°C[a]
Boiling point	–4.5°C at 760 mm Hg[a]
Log K_{ow}	1.99[b]
Water solubility	0.735 g/L at 20°C[a]
Vapor pressure	2,110 mm Hg at 25°C[a]
Vapor density relative to air	1.87[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

1,3-Butadiene is used primarily as a monomer to manufacture many different types of polymers and copolymers and as a chemical intermediate to produce a number of important industrial chemicals. More than 75% of the 1,3-butadiene produced goes into synthetic rubber products (CEN 1986). The major uses include production of styrene-butadiene rubber (30% to 35%), polybutadiene rubber (20% to 22%), adiponitrile (12% to 15%), styrene-butadiene latex (10%), neo-

prene rubber (5% to 6%), acrylonitrile-butadiene-styrene resins (5% to 6%), and nitrile rubber (3%), exports (4%), and other uses, including production of specialty polymers (2% to 8%) (IARC 1992, ATSDR 1993). The major end-use products containing styrene-butadiene and polybutadiene are tires. Other products include latex adhesives, seals, hoses, gaskets, various rubber products, nylon carpet backings, paper coatings, paints, pipes, conduits, appliance and electrical equipment components, automotive parts, and luggage. The only major nonpolymer use is in the manufacture of adiponitrile, a nylon intermediate. Butadiene is also used in the manufacture of the fungicides captan and captafol (Morrow 1990, IARC 1992, Kirschner 1996).

Production

1,3-Butadiene is isolated by distillation or extraction from crude butadiene, which is a by-product of ethylene production. Commercial production began in the 1930s (IARC 1992). Between 1980 and 2002, annual U.S. production of rubber-grade 1,3-butadiene ranged from a low of 869,000 metric tons (1.9 billion pounds) in 1982 to a high of 2,009,000 metric tons (4.4 billion pounds) in 2000 (IARC 1992, CEN 1999, 2003). The average annual change was about 2.5% from 1992 to 2002 compared with about 1.2% from 1980 to 1990. 1,3-Butadiene ranked 34th among the top 50 chemical commodities produced in the United States in 1987, falling to 36th by the mid 1990s (Morrow 1990, Kirschner 1996, CEN 1997). In 1990, 30 ethylene plants in the United States produced crude butadiene streams that were processed in 11 extraction plants (Morrow 1990). In 2009, 11 U.S. producers and 12 U.S. suppliers of 1,3-butadiene were identified (ChemSources 2009, SRI 2009). Because U.S. demand for 1,3-butadiene has exceeded the domestic supply in most years, imports have greatly exceeded exports. Annual U.S. imports ranged from 500 million to 900 million pounds from the late 1970s to the mid 1980s and from 1.2 billion to 1.4 billion pounds from 1998 to 2000, decreasing to 200 million pounds in 2002 (ATSDR 1993, USITC 2009). In 2008, imports were 1.7 billion pounds. Annual U.S. exports ranged from 94 million to 145 million pounds from the late 1970s through the mid 1980s, decreasing to 37.6 million pounds in 2000 and 15.2 million pounds in 2002. In 2008, exports were 217.6 million pounds.

Exposure

The primary route of potential exposure to 1,3-butadiene for the general population is inhalation. Some exposure may occur through ingestion of contaminated food or water or dermal contact; however, these routes of exposure are unlikely under most circumstances. 1,3-Butadiene is not a common contaminant of water supplies. Although some food packaging contains residual 1,3-butadiene, the available data indicate that it does not usually migrate to the food. Certain cooking oils, such as rapeseed oil (canola), release 1,3-butadiene when heated (Shields *et al.* 1995).

Most people are exposed to low levels of 1,3-butadiene in the air, because it is released to the environment during its production, use, storage, and disposal and is present in gasoline, automobile exhausts, and cigarette smoke. 1,3-Butadiene is emitted from petroleum refineries and from furnaces at secondary lead smelting facilities handling automotive lead-acid batteries that contain plastic battery separators or that have hard rubber casings (EPA 1996). Incomplete combustion of a variety of fuels forms 1,3-butadiene as a product. 1,3-Butadiene makes up 0.5% to 2% of the total organic gas emissions from most types of combustion (Ligocki *et al.* 1994). It can also be found in motor-vehicle exhaust emissions as a product of incomplete combustion of gasoline and diesel oil and from the thermal breakdown of plastics (ATSDR 1993, EPA 1996). Through modeling of dispersion from a typical freeway source in California, it was estimated that gasoline-fueled vehicles emit 0.011 g of 1,3-butadiene per mile (Cooper and Reisman 1992). 1,3-Butadiene also is formed naturally as a by-product of forest fires (HSDB 2009). Releases of 1,3-butadiene in sidestream cigarette smoke into the air have been variously estimated at 152 to 400 μg per cigarette (Ligocki *et al.* 1995). Calculations based on 400 μg per cigarette indicate that 1,3-butadiene concentrations in the homes of smokers would be increased by approximately 4 $\mu g/m^3$, and concentrations in air at workplaces allowing smoking would be increased by 13 $\mu g/m^3$ (Wallace 1991).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, total industrial environmental releases of 1,3-butadiene declined from more than 7.7 million pounds in 1988 to about 1.8 million pounds in 2007, of which over 90% was released to air (TRI 2009). However, a nationwide 1,3-butadiene inventory (including vehicle emissions and emissions from manufacturing and producing facilities) calculated annual butadiene emissions to air to be 102 million kilograms (225 million pounds) in 1990 (Ligocki *et al.* 1994), considerably higher than EPA's estimate of about 5.2 million pounds (2.4 million kilograms) for industrial emissions in the same year.

The median daily concentrations of 1,3-butadiene in U.S. ambient air samples collected from 1970 to 1987 were 0.29 ppb in urban areas (385 samples), 0.32 ppb in suburban areas (196 samples), and 0.1 ppb in rural areas (2 samples). The maximum 24-hour average concentrations of 1,3-butadiene reported for four U.S. cities in 2004 were 0.3 ppb for St. Louis, Missouri, 0.5 ppb for Chicago, Illinois, and Los Angeles, California, and 37.4 ppb for Houston, Texas (Clements *et al.* 2006). However, reported average daily concentrations of 1,3-butadiene in ambient air within a mile of petrochemical facilities have exceeded 100 ppb, and the highest hourly average concentrations have exceeded 900 ppb (ATSDR 1993). Volatilization of 1,3-butadiene from wastewaters of styrene-1,3-butadiene copolymer production at publicly owned treatment works has been calculated to be 21 tons per year (EPA 1996).

Occupational exposure to 1,3-butadiene may occur through inhalation and, to a lesser extent, dermal contact (NTP 1984). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that about 52,000 workers at 2,201 facilities, including 1,410 women, potentially were exposed to 1,3-butadiene (NIOSH 1990). This estimate does not include workers exposed to butadiene polymers and copolymers and is consistent with an earlier an estimate of about 66,000 to 70,000 workers at 3,086 facilities reported in the National Occupational Hazard Survey (conducted from 1972 to 1974) (NIOSH 1976). Health hazard evaluation surveys conducted by the National Institute for Occupational Safety and Health at six facilities found air concentrations of 1,3-butadiene ranging from 0.06 to 39 ppm. Surveys conducted at many monomer, polymer, and end-user plants have reported concentrations ranging from below detection to 374 ppm (827 mg/m^3). In most cases, 8-hour time-weighted-average concentrations were less than 10 ppm (< 22 mg/m^3) (IARC 1992, ATSDR 1993). For the monomer industry as a whole, 1,3-butadiene concentrations were greater than 10 ppm (> 22 mg/m^3) in 7.1% of the samples, 2 to 10 ppm (4 to 22 mg/m^3) in 12.8%, 1 to 2 ppm (2 to 4 mg/m^3) in 12.3% and less than 1 ppm (< 2 mg/m^3) in 67.8%. The Occupational Safety and Health Administration permissible exposure limit is 1 ppm. For the polymer industry as a whole, the corresponding percentages for these four ranges were 3.3%, 7.7%, 3.3%, and 85.8%, respectively. The arithmetic mean exposure for personal full-shift exposures in the polymer plants was 1.14 ppm (2.57 mg/m^3) (Fajen *et al.* 1993).

Regulations

Department of Transportation (DOT)

Butadienes are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.
National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of 1,3-butadiene is subject to certain provisions for the control of volatile organic compound emissions.
Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.
Standards have been established for emissions of 1,3-butadiene from reformulated gasoline and motor vehicles.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 1 ppm.
Short-term exposure limit (STEL) = 5 ppm.
Comprehensive standards for occupational exposure to 1,3-butadiene have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,000 ppm.
Listed as a potential occupational carcinogen.

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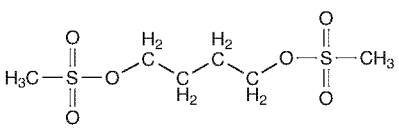
1,4-Butanediol Dimethanesulfonate

CAS No. 55-98-1

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as busulfan; trimethylene methanesulfonate; Busulfex, a registered trademark of Otsuka Pharmaceutical Co., Ltd.; or Myleran, a registered trademark of GlaxoSmithKline, LLC



Carcinogenicity

1,4-Butanediol dimethanesulfonate is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Cases of cytological abnormalities (e.g., giant nuclei, cytomegaly, and dysplasia) and cancer at several different tissue sites, including the breast and female genital organs, were reported among leukemia patients who had been treated with 1,4-butanediol dimethanesulfonate. In a follow-up study of bronchial-cancer patients randomly assigned to treatment with Myleran, cyclosphosamide, or placebo after surgical removal of the tumor, leukemia developed in patients who had received Myleran only, without radiation or other cytotoxic agents; however, the risk of leukemia was not dose-related (IARC 1987).

Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of 1,4-butanediol dimethanesulfonate in experimental animals is limited. 1,4-Butanediol dimethanesulfonate administered to mice by intraperitoneal injection caused leukemia in one study and T-cell lymphoma in another, but did not increase the incidences of tumors in two other studies. When administered by intravenous injection to female mice, 1,4-butanediol dimethanesulfonate caused thymic lymphoma and ovarian tumors. One study reported that pulmonary lesions (including benign tumors) developed in mice exposed to 1,4-butanediol dimethanesulfonate, but the route of administration was not specified. In rats, 1,4-butanediol dimethanesulfonate did not cause tumors when administered orally. When administered intravenously, it was reported to cause a variety of tumors in male rats, but this study could not be evaluated because of incomplete reporting (IARC 1982, 1987).

Properties

1,4-Butanediol dimethanesulfonate is an alkylsulfonate alkylating agent that exists at room temperature as an off-white granular powder with a slight odor. It has a molecular weight of 246.3 and a melting point of 119°C. It is almost insoluble in water, sparingly soluble in acetone, and slightly soluble in ethanol, and it hydrolyzes in aqueous solution (IARC 1974, Akron, 2009).

Use

1,4-Butanediol dimethanesulfonate is used as a chemotherapeutic agent to treat some forms of leukemia, particularly chronic myelocytic leukemia (IARC 1974, 1982). It also may be used in combination with cyclophosphamide as a conditioning regimen prior to bone marrow transplants for chronic myelogenous leukemia. It is given in tablets or by intravenous injection (FDA 2009, MedlinePlus 2009).

Production

Total annual production of 1,4-butanediol dimethanesulfonate was believed to be less than 500 kg (1,100 lb) in 1974 (IARC 1974). In 2009, no producer of 1,4-butanediol dimethanesulfonate was identified worldwide (SRI 2009), but it was available from 14 U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing 1,4-butanediol dimethanesulfonate as the active ingredient were produced by two U.S. pharmaceutical companies (FDA 2009). No data on U.S. imports or exports of 1,4-butanediol dimethanesulfonate were found.

Exposure

Patients may be exposed to 1,4-butanediol dimethanesulfonate by ingestion or intravenous administration during chemotherapeutic treatment. 1,4-Butanediol dimethanesulfonate is available as 2-mg oral tablets or in injectable form (6 mg/mL) (FDA 2009). The typical dosage in tablet form is 4 to 8 mg daily (IARC 1974). The recommended intravenous dose prior to a bone-marrow transplant is 0.8 mg/kg of body weight given as a two-hour infusion every six hours for four days (RxList 2010). Occupational exposure could occur among workers formulating or packaging the tablets or health-care professionals administering the drug. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,764 workers, including 892 women, potentially were exposed to 1,4-butanediol dimethanesulfonate (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Regulated as a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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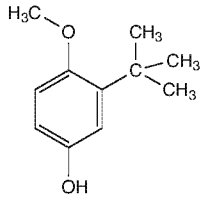
Butylated Hydroxyanisole

CAS No. 25013-16-5

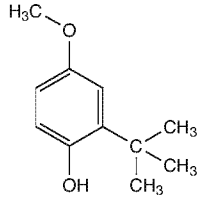
Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as BHA or or (1,1-dimethylethyl)-4-methoxyphenol



2-BHA



3-BHA

Carcinogenicity

Butylated hydroxyanisole (BHA) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to BHA caused benign and malignant tumors of the forestomach (papilloma and squamous-cell carcinoma) in rats of both sexes and in male mice and hamsters (IARC 1986, Masui *et al.* 1986). Since BHA was listed in the *Sixth Annual Report on Carcinogens,* an additional study in experimental animals has been identified. Dietary administration of BHA to fish (hermaphroditic *Rivulus marmoratus*) as larvae caused liver cancer (hepatocellular carcinoma) in the adult fish (Park *et al.* 1990).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to BHA. Since BHA was listed in the *Sixth Annual Report on Carcinogens,* one epidemiological study of BHA has been identified. A population-based nested case-control study of stomach cancer in men and women within the Netherlands Cohort Study of dietary intake found no increase in risk at typical levels of dietary intake of BHA (Botterweck *et al.* 2000).

Properties

BHA is an antioxidant which exists at room temperature as a white or slightly yellow, waxy solid with a faint characteristic odor (IARC 1986). BHA in commercial use consists of a mixture of 3-*tert*-butyl-4-hydroxyanisole (3-BHA) and 2-*tert*-butyl-4-hydroxyanisole (2-BHA). BHA is insoluble in water, but is soluble in fats, oils, propylene glycol, petroleum ether, chloroform, and 50% alcohol. Physical and chemical properties of BHA are listed in the following table.

Property	Information
Molecular weight	180.2[a]
Melting point	48°C to 55°C[a]
Boiling point	264°C to 270°C at 733 mm Hg[a]
Log K_{ow}	3.5[b]
Water solubility	0.213 g/L at 25°C[b]
Vapor pressure	0.00248 mm Hg at 25°C[a]

Sources: [a]HSDB 2009, [b]ChemIDplus 2009.

Use

BHA is used primarily as an antioxidant and preservative in food, food packaging, animal feed, and cosmetics, and in rubber and petroleum products (IARC 1986). Food-grade BHA contains over 85% 3-BHA and less than 15% 2-BHA, while cosmetic-grade BHA contains 90% 3-BHA and 8% 2-BHA. Since 1947, BHA has been added to edible fats and fat-containing foods for its antioxidant properties. It is also used in foods cooked or fried in animal oils, because of its high thermal stability and its ability to remain active in baked and fried foods (HSDB 2009). BHA is added to butter, lard, meats, cereals, baked goods, sweets, beer, vegetable oils, potato chips, snack foods, nuts and nut products, dehydrated potatoes, and flavoring agents. It is used in sausage, poultry and meat products, dry mixes for beverages and desserts, glazed fruits, chewing gum, active dry yeast, defoaming agents for beet sugar and yeast, and emulsion stabilizers for shortening (IARC 1986). BHA stabilizes the petroleum wax coatings of food packaging (HSDB 2009). BHA is considered by the U.S. Food and Drug Administration (FDA) to be generally recognized as safe when the antioxidant content does not exceed 0.02% by weight of the food's total fat or oil content.

BHA is one of the primary antioxidants used in feeds, because it retards the oxidation of vitamin A, fats, and vegetable oils. It is an effective stabilizer for essential oils, paraffin, and polyethylenes (HSDB 2009). It is used as an antioxidizing agent in a biomaterial made from polyurethane and polyethylene oxide used to make mainline catheters (Silverstein *et al.* 1997). BHA is used as a preservative and antioxidant in pharmaceutical preparations and cosmetic formulations containing fats and oils. A 1981 FDA survey found that BHA was used in 3,217 of 21,279 cosmetic formulations; the majority (88%) of the reported concentrations did not exceed 0.1%. In that survey, use of BHA was highest in lipstick formulations (1,256 products), followed by eye-shadow products (410) (IARC 1986). For industrial use, BHA has largely been replaced by *tert*-butylhydroquinone.

Production

In 2009, no producers of BHA were identified worldwide (SRI 2009), but it was available from 46 suppliers, including 18 U.S. suppliers (ChemSources 2009). No recent data on U.S. imports or exports of BHA were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of BHA totaled 10,000 to 500,000 lb in 1986 and 2000, 1 million to 10 million pounds in 1996, and less than 500,000 lb in 2006 (EPA 2004, 2009).

Exposure

Routes of human exposure to BHA are ingestion, inhalation, and dermal contact. In 1975, the estimated average daily intake of BHA in the diet was 4.3 mg (IARC 1986). Estimated annual U.S. use of BHA in food increased from 170,000 kg (374,000 lb) in 1960 to 300,000 kg (660,000 lb) between 1970 and 1982 (IARC 1986). Total reported annual use of BHA in the mid 1970s was 450 metric tons (990,000 lb) (Nicholas *et al.* 1978). The concentration of BHA in six samples of human adipose tissue ranged from 0.01 to 0.03 ppm (Conacher *et al.* 1986). Dermal exposure to BHA occurs from its use as an antioxidant in cosmetic products, especially lipstick and eye shadow (IARC 1986). BHA is also used as an antioxidant for some rubber and petroleum products, and it is a stabilizer for vitamin A (HSDB 2009).

Workers potentially are exposed to BHA in certain industries, including food producers, animal feed producers, livestock producers, cosmetic manufacturers, some petroleum workers, and rubber producers and those who handle the end products, such as tires. Fast-food service personnel who normally cook and serve fried and oily foods potentially are exposured to BHA at high levels; BHA is volatile at 150°C to 170°C (302°F to 338°F) and is readily lost from thermal processes that generate steam (Warner *et al.* 1986). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 89,673 workers, including 44,061 women, potentially were exposed to BHA. Most of these workers were in the Health Services (> 24,000 workers), Food (> 18,000 workers), and Chemical and Allied Products industries (> 13,000 workers) (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

BHA is generally recognized as safe for use in food when the total of antioxidants is not greater than 0.02% of fat or oil content.

BHA may be used as a food additive permitted for direct addition to food for human consumption as prescribed in 21 CFR 172 and 166.

BHA may be used in the manufacture of food packaging materials, with a limit of addition to food of 0.005%.

BHA may be used as an antioxidant in defoaming agents for processed foods, not to exceed 0.1% by weight of defoamer.

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Cadmium and Cadmium Compounds

CAS No. 7440-43-9 (Cadmium)

No separate CAS No. assigned for cadmium compounds as a class

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as Cd

Carcinogenicity

Cadmium and cadmium compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. Cadmium and cadmium compounds were first listed as *reasonably anticipated to be human carcinogens* in the *First Annual Report on Carcinogens* in 1980, based on sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be human carcinogens* in the *Ninth Report on Carcinogens* in 2000.

Cancer Studies in Humans

Several epidemiological cohort studies of workers found that exposure to various cadmium compounds increased the risk of death from lung cancer (IARC 1993). Although other factors that could increase the risk of cancer, such as co-exposure to arsenic, were present in several of these studies, it is unlikely that the increased risk of lung cancer was due entirely to confounding factors. Follow-up analysis of some of these cohorts has not definitively eliminated arsenic exposure as a possibly confounding factor, but has confirmed that cadmium exposure is associated with elevated lung-cancer risk under some industrial circumstances (Sorahan *et al.* 1995, Sorahan and Lancashire 1997). Some early cohort studies found an increased risk of death from prostate cancer among cadmium-exposed workers, but later cohort studies have not confirmed this observation. Additional epidemiological evidence (including case-control studies and geographic-distribution studies) suggests an association between cadmium exposure and cancer of the prostate (Bako *et al.* 1982, Shigematsu *et al.* 1982, Garcia Sanchez *et al.* 1992, van der Gulden *et al.* 1995), kidney (Kolonel 1976, Mandel *et al.* 1995), and urinary-bladder (Siemiatycki *et al.* 1994). The International Agency for Research on Cancer reevaluated the evidence for carcinogenicity of cadmium in 2009 and reaffirmed its earlier conclusion that there was sufficient evidence of cadium's carcinogenicity in humans. The evidence was classified as sufficent for lung cancer and limited for prostate and kidney cancer (Straif *et al.* 2009).

Studies on Mechanisms of Carcinogenesis

Many studies of cultured mammalian cells have shown that cadmium compounds cause genetic damage, including gene mutations, DNA strand breaks, chromosomal damage, cell transformation, and disrupted DNA repair. Increased frequencies of chromosomal aberrations have been observed in the lymphocytes of workers occupationally exposed to cadmium. The accumulated information, including the carcinogenicity of a wide variety of cadmium compounds, supports the conclusion that ionic cadmium is the genotoxic form of cadmium and its compounds. Therefore, the carcinogenic potential of a given cadmium compound is expected to depend on the degree to which the compound releases ionic cadmium under the conditions of exposure (IARC 1993).

The sensitivity of cells or tissues to cadmium appears to be related, at least in part, to their ability to produce metallothionein, a protective protein that binds heavy metals, including cadmium. Activation of the *MT* gene in response to cadmium exposure results in production of metallothionein, which sequesters cadmium, thus limiting its genotoxic effects. The difference between rats and mice in sensitivity to cadmium as a lung carcinogen appears to be due to differential expression of *MT* in lung tissue following inhalation exposure to cadmium. Other tissues in which cadmium causes cancer in rodents also show minimal basal expression of the *MT* gene or limited activation of *MT* in response to cadmium exposure (Oberdörster *et al.* 1994). There is no evidence to suggest that mechanisms by which cadmium causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Experimental Animals

Cadmium compounds caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Exposure to various cadmium compounds by inhalation or intratracheal instillation caused lung cancer (pulmonary adenocarcinoma) in rats; tumor incidence increased with increasing exposure level. Lung tumors were also observed occasionally in mice exposed to cadmium compounds by inhalation (IARC 1993). When administered orally to rats, cadmium chloride caused dose-related increases in the incidences of leukemia and benign testicular tumors. In several studies with rats and mice, single or multiple injections (subcutaneous, intramuscular, or intraperitoneal) of various soluble and insoluble cadmium compounds caused tumors (sarcoma) at the injection site (IARC 1993, Waalkes and Rehm 1994a).

Subcutaneous injection of cadmium compounds caused tumors at various tissue sites, including prostate tumors in rats, testicular tumors in rats and mice, lymphoma in mice, adrenal-gland tumors in hamsters and mice, and lung and liver tumors in mice (IARC 1993, Waalkes *et al.* 1994, Waalkes and Rehm 1994a,b,c).

Since cadmium and cadmium compounds were listed in the *Ninth Report on Carcinogens,* additional studies in rats have been identified. Subcutaneous administration of cadmium chloride to rats caused pituitary-gland tumors (Waalkes *et al.* 1999a). In rats orally exposed to cadmium chloride, the incidence of kidney tumors increased with increasing exposure level; however, the tumor incidence was not significantly higher at the highest dose than in the unexposed control animals (Waalkes *et al.* 1999b).

Properties

Cadmium is an odorless, silver-white, blue-tinged malleable metal or grayish-white powder. It has an atomic weight of 112.4 and belongs to group IIB of the periodic table. Almost all cadmium compounds have an oxidation state of +2. Cadmium is soluble in dilute nitric acid, ammonium nitrate, and hot sulfuric acid and insoluble in water. It is slowly oxidized in moist air but forms cadmium oxide fumes when heated. Cadmium and cadmium compounds are not combustible but may decompose in fires and release corrosive and toxic fumes. Hot cadmium metal reacts with halogens, phosphorus, selenium, sulfur, and tellurium, and cadmium vapor reacts with oxygen, carbon dioxide, water vapor, sulfur dioxide, sulfur trioxide, and hydrogen chloride. Cadmium is commercially available in purities ranging from 99% to 99.9999%, as powders, foils, ingots, slabs, sticks, and crystals (IARC 1993, Llewellyn 1994, HSDB 2009).

Commercially important cadmium salts include cadmium chloride, cadmium sulfate, and cadmium nitrate. Cadmium chloride occurs as small colorless-to-white rhombohedral or hexagonal crystals. It is soluble in water and acetone, slightly soluble in methanol and ethanol, and insoluble in diethyl ether. Commercial cadmium chloride is a mixture of hydrates similar to the dihydrate form of cadmium chloride. It is available in purities ranging from 95.0% to 99.999%. Cadmium sulfate occurs as colorless to white orthorhombic crystals. It is soluble in water but insoluble in ethanol, acetone, and ammonia, and is available in purities ranging from 98% to 99.999%. Cadmium nitrate occurs as a colorless solid. It is soluble in water, ethanol, acetone, diethyl ether, and ethyl acetate, and very soluble in dilute acids. Cadmium nitrate is available in technical and reagent grades with a purity of 99% or higher (IARC 1993, HSDB 2009).

Other commercially important cadmium compounds include cadmium oxide and cadmium sulfide. Cadmium oxide occurs as a colorless amorphous powder or dark-brown crystals. It is practically insoluble in water, soluble in dilute acids and ammonium salts, and insoluble in alkalis. Commercial-grade cadmium oxide is available in purities ranging from 99% to 99.9999%. Cadmium sulfide occurs as yellow-orange hexagonal or cubic dimorphic semitransparent crystals or as a yellow-brown powder, but may be prepared to range in color from white to deep orange-red. It is practically insoluble in water, insoluble in alkalis, slightly soluble in ammonium hydroxide, and soluble in concentrated or warm dilute mineral acids, with evolution of hydrogen sulfide. Cadmium sulfide is available in purities ranging from 98% to 99.999%; however, many cadmium sulfide products are complex mixtures that contain other metal compounds (IARC 1973, 1993, HSDB 2009).

Use

Cadmium was discovered in 1817 but was not used commercially until the end of the 19th century. The earliest use of cadmium, primarily in the sulfide form, was in paint pigments. Minor amounts were used in dental amalgams in the early 1900s. During World War I, cadmium was used as a substitute for tin. Since World War II, almost all cadmium has been used in batteries, pigments, alloys, electroplating and coating, and stabilizers for plastics (IARC 1993, Llewellyn 1994). However, in the late 20th century, the percentage of cadmium consumed globally in the production of nickel-cadmium (NiCd) batteries increased, while the percentages used in other traditional end uses declined dramatically because of environmental and health concerns (Tolcin 2009b). Electroplating and coating accounted for more than half of cadmium consumption in 1960 but declined to 8% by 2000. Cadmium pigments accounted for 20% to 30% of cadmium consumption between 1970 and 1990 but declined to 12% in 2000. From 1970 to 2000, cadmium's use in stabilizers decreased from 23% to 4%, and its use in alloys from 8% to 1%. In contrast, cadmium's use in batteries grew from 8% in 1970 to 75% in 2000 (IARC 1993, Plachy 2000). In 2009, NiCd battery production was the leading end use of cadmium, followed by pigments, coatings and plating, stabilizers for plastics, nonferrous alloys, and other specialized uses (Tolcin 2009a).

Cadmium chloride is used in electroplating, photocopying, calico printing, dyeing, mirrors, analytical chemistry, vacuum tubes, and lubricants and as a chemical intermediate in production of cadmium-containing stabilizers and pigments (IARC 1993, HSDB 2009). However, its uses are declining. Cadmium chloride was used as a fungicide for golf courses and home lawn turf, but these uses were banned by the U.S. Environmental Protection Agency in the late 1980s (ATSDR 1999). Cadmium sulfate is used in electroplating, fluorescent screens, vacuum tubes, and analytical chemistry; as a chemical intermediate to produce pigments, stabilizers, and other cadmium compounds; as a fungicide or nematocide; and as an electrolyte in Weston cells (portable voltage standards). Cadmium nitrate is used in photographic emulsions, to color glass and porcelain, in nuclear reactors, and to produce cadmium hydroxide for use in alkaline batteries (IARC 1993, HSDB 2009).

Cadmium sulfide is used primarily in pigments for paints, glass, ceramics, plastics, textiles, paper, and fireworks. It is also used in solar cells, fluorescent screens, radiation detectors, smoke detectors, electron-beam-pumped lasers, thin-film transistors and diodes, phosphors, and photomultipliers. Cadmium oxide is used primarily in NiCd batteries, but also as a catalyst and in electroplating, electrical contacts, resistant enamels, heat-resistant plastics, and manufacture of plastics (such as Teflon) and nitrile rubbers. Cadmium oxide has been used as a nematocide and ascaricide in swine (IARC 1993, HSDB 2009).

Production

Cadmium is a rare element, not found in its pure state in nature. It occurs mainly as cadmium sulfide (CdS, or greenockite) in zinc deposits. Cadmium is chiefly recovered as a by-product of zinc concentrates, and its production depends on the demand for zinc (Llewellyn 1994). The United States began commercial production of cadmium in 1907 and was the world's leading producer from 1917 to the late 1960s. U.S. cadmium production peaked in 1969, at 5,740 metric tons (12.7 million pounds) (USGS 2009). Average annual production levels fell to 2,758 metric tons (6 million pounds) for the 1970s, 1,498 metric tons (3.3 million pounds) for the 1980s, 1,437 metric tons (3.2 million pounds) for the 1990s, and 1,196 metric tons (2.6 million pounds) for the 2000s (Tolcin 2009a, USGS 2009). In 2009, the United States and India each produced 700 metric tons (1.54 million pounds) of cadmium, tying them as the ninth-largest producers of cadmium globally (Tolcin 2009a). U.S. production accounted for almost 4% of 2009 world cadmium production. U.S. production of cadmium compounds